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SYMPOSIUM ON THE RECENT ADVANCES IN THE MEDICAL SCIENCE

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ADVANCES IN PUBLIC HEALTH

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Public health has passed its adolescent stage and is emerging into maturity as a positive science. The scientific advancements of the past quarter century have brought with them a phase of public health consciousness on the part of the medical profession as well as the general public, with the result that tools have been developed whereby the health of the people as a whole has been improved. Withal, we are only beginning the battle against disease and the next few years will see many more advancements.

New case finding techniques in tuberculosis are being expanded, mainly in the field of mass x-ray procedures. With the use of microphotofluorographic equipment, large numbers of persons can be screened effectively and at relatively low cost. The follow-up of suspects and cases includes the examination of contacts, along with education in prevention and treatment. Increasing emphasis is being placed on the finding of early cases in a wholehearted effort to cure and rehabilitate, so that patients may become self-supporting and useful members of society.

Research goes on in the use of aluminum in the prevention and treatment of silicosis, where evidence, available to date, indicates aluminum therapy is of therapeutic significance. It is recommended, however, that the general application of aluminum therapy in industry be delayed until adequately and impartially controlled clinical observation demonstrates a practicable effectiveness. In the meantime, there should be no slackening in the control measures that have been found to accomplish a reduction of the hazards of harmful dusts in industry.

During the past few years great strides have been made in the control of communicable diseases. To name but a few . . . , a significantly effective influenza vaccine has been developed, and diphtheria toxoid has been combined successfully with tetanus and whooping cough immunizing agents. It is noteworthy that, because of complete immunization by the Army and Navy, tetanus was extremely rare in the armed forces during the recent conflict. Recent developments have given us an immune globulin for the prophylaxis and treatment of measles which may have far-reaching possibilities in this, as well as other fields in pediatrics. Research goes on with penicillin, its usefulness already having been established in reducing the period of communicability of certain of the more common infections, and in reducing the hazards of complications.

Penicillin also permits the safe and effective rapid treatment of syphilis and gonorrhea, allowing more emphasis to be placed by public health agencies on case finding. The main value of the short-term therapy of syphilis is the reduction in the proportion of lapses from treatment, so frequent in long-term standard therapy. However, in the manufacture of penicillin for commercial use, certain refinements have lowered its curative value for syphilis. Knowing that factors F and G are essential for the successful treatment of this disease, and that factor K is the least effective, methods have been developed during the past year to inhibit the formation of the K factor. At the present time, a considerable amount of commercial penicillin containing an abundance of the K factor and deficient in F and G is on the market, thus necessitating relatively larger doses of the drug to effect cure.

The diagnosis of syphilis is primarily a laboratory procedure and the recently developed cardiolipin antigen can be set at a stable sensitivity level, while increasing specificity, giving cause for hope of enhancing the reliability of serodiagnostic methods. Cardiolipin, however, is still definitely experimental, but, if proven, may result in a complete overhaul in the field of syphilis serology.

The extent of the toxicity to human beings of D.D.T. (dichloro-diphenyl-trichloroethane) is not known, but it has been found that it can be used in the control of insects with little danger to the user if reasonable precautions are observed. Perhaps in this country it will find its greatest use in the control of malaria. At the present time, the U. S. Public Health Service is engaged in an anophelene mosquito control program in the endemic areas of the southern states, putting to use practices found effective by our armed forces. D.D.T. is also being used effectively in the control of the vectors typhus and yellow fever. It must be remembered, however, that though D.D.T. may prove to be a boon to humanity, it must not be regarded as a substitute for sanitation.

In the field of dental health, the discovery that the topical application of a two per cent solution of fluorine reduces the incidence of dental caries by approximately fifty per cent, offers great possibilities. Perhaps we may be justified in assuming that in the not too distant future, caries will be a minor instead of a major problem in oral health.

One of the important causes of death in childhood is rheumatic fever, and although it is not known as yet, with certainty, whether rheumatic fever programs are preventing illness or prolonging lives, substitution of good management for the neglect or over protection which frequently characterizes the handling of these children, is enough to make these programs worthwhile. Realizing the need for better and more widely available consultative services for rheumatic fever, as well as coordinated services for the care of patients, health departments are encouraging the development of such facilities. In some instances, clinics are being organized independently by local medical associations and hospital staffs, working cooperatively with local or state health departments in case finding, follow-up and education.

The outlook for the control of cancer is definitely improving. There is growing evidence that cancer patients are seeking medical care earlier in the course of their disease, enhancing their chances of survival. This trend is due in most part to public education. Even in the present state of our knowledge, many lives could be saved annually by earlier diagnosis and with the institution of appropriate treatment. The ultimate answer, however, lies in the laboratory.

Today, public health has developed to the point where it has become apparent that many diseases cannot be controlled without full citizen understanding and participation, and therefore health education is coming to be universally accepted as an essential part of every public health program. To stimulate public action and individual participation, well planned and coordinated programs of education are required. Three major methods are employed in health education, namely:

as a part of teaching in the schools and colleges, health information for the general public; and health teaching by those who are actually engaged in giving medical care to the sick. This latter is one of the great responsibilities and privileges of the practitioner of medicine.

It is generally accepted that some method is needed for distributing the risks in sickness and the costs of medical care, so that the population as a whole can gain access to medical services as needed. Insurance and taxation are the two methods of distributing costs. Both are employed in this country, but as yet only for special groups of people or for particular types of care, usually hospitalization. Plans for insurance are faulty in many respects in that they do not offer comprehensive medical care, provide for no prevention or control of disease, are not really plans for medical service but for financing general hospitalization and surgery. Because of variations in the types of services offered by the 219 plans for prepaid hospitalization in this country, it is impossible to compute any arithmetic totals of service furnished by them.

The year 1945 was revolutionary inasmuch as it witnessed the publication of two books which bared the shortcomings of public health facilities as provided by official and voluntary health agencies. Reference is made to the report of the Commonwealth Fund by Haven Emerson, M.D., entitled "Local Health Units for the Nation," which reviews the organization and management of the health departments of each of the 48 states and gives recommendations for improvement in service; and the Gunn-Platt report, "Voluntary Health Agencies—An Interpretive Study," made under the auspices of the National Health Council. This latter report is a critical review of the services available through health agencies throughout the nation which are dependent upon voluntary contributions for survival. Both reports are serving a useful purpose inasmuch as they expose the weaknesses of existing health services organized entirely for the benefit of the people, and dependent entirely upon the people for support, whether supported through taxation or by voluntary contribution.

The contemporary health services offered in our nation, supply only about two-thirds of the population with adequate full-time local health protection, while approximately 40 million persons are excluded for one reason or another. The question which faces all those interested or participating in the provision of public health services seems to be—can we move on into the realm of attaniable possibilities and meet the needs and wishes of the people to the achievement of still higher levels of human health and welfare?

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UROLOGY

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Advancements in the field of urology have been made (1) the treatment of urinary calculi, (2) carcinoma of the bladder, and (3) carcinoma of the prostate. The treatment of urinary infection with penicillin and streptomycin has specific applications in urology, but they also have many general applications and therefore will not be discussed. There have been many technical improvements in the older methods of therapy and diagnosis which are unsuitable for discussion.

The cause of urinary calculi has been studied from the standpoint of calcium metabolism and endocrines. The most specific advancement in the cause of stone formation has been made by Albright (1). In a study of 23 cases of hyperparathyroidism he found 15 patients to harbor renal calculi and three other patients had renal leisons due to calcium deposits in the renal tubules. Hyper-secretion of the parathyroids results in increased calcium and decreased phosphorus in the blood. It is an excellent example of what may happen when a kidney has to deal with a blood stream which is laden with calcium. Bone diseases and immobilization of the patient may result in increased urinary calcium which is derived from decalcification of the bone. The increased excretion of uric acid, oxalates, and the presence of cystin in the urine are other examples of hyper-excretion of a specific salt which may result in stone formation.

There is a great deal of difference of opinion as to the frequency with which hyperparathyroidism occurs as an etiological factor in the formation of renal calculi. This phase of the disease has been stressed by Albright et al. from the Mass. General Hospital. From 1930 to 1937 in a study of 36 cases of hyperthyroidism, Chute (2) found calculi formation in 83% of them and the disease to be bilateral in 53%. Braasch (3) at the Mayo Clinic found but two cases of proved hyperparathyroidism in 1,206 patients suffering from calculus disease. Higgins (4) at the Cleveland Clinic found the disease in only one-tenth of one per cent of stone patients.

Regardless of the wide difference of opinion as to the frequency of hyperparathyroidism in stone formation, one fact seems to stand out and that is that where hypercalcinuria occurs stone formation may result. This is substantiated by Flocks (5) who found that 66% of stone cases showed increased urinary calcium and in a great number of them none of the causes of excess calcium excretion was discoverable.

The above facts have stressed the etiology of certain varieties of stone formation due to excess of calcium excretion by the kidney. Advantage of this knowledge has been taken in the prevention and treatment of stone formation. It has long been known that the pH of the urine is a factor in the type of stone formation which will occur. Thus with a pH of 5 a uric acid stone should form; whereas with a pH of 8 calcium carbonate and phosphatic stones occur. It would seem that with a reversal of the pH of the urine, in the examples cited above, it should be of aid in the dissolution and prevention of these stones. Within certain limits this is true.

In those calcium and phosphatic stones in which hypercalcinuria plays a part, the administration of acidifing drugs and the so-called "acid ash diet" have been shown by Albright and Flocks to defeat their purpose, in that their administration results in increased absorption of calcium from the tissues and increased excretion of calcium by the kidney. This is especially so where stone formation is taking place in the presence of urea splitting organisms, where it is impossible to render the urine acid. These procedures are definitely contraindicated, because, bringing

more calcium to the infection means more rapid stone formation. It is evident that the purpose of this type of medication is to decrease the precipitation of calcium and phosphatic salts at the kidney level and thereby prevent stone formation.

Shorr (6) . . . believed that the less calcium and phosphates the kidney had to dispose of, would also lessen the possibilities of stone formation. He lowered the calcium and increased the citric acid content of the urine by the use of estrogens. Estrogens increase the excretion of citric acid and the citrates combine with calcium to form a soluble calcium-citrate complex instead of an insoluble calcium phosphate. He diverted the excretion of phosphate from the kidney to the intestinal tract by the use of aluminum hydroxide gel. By the use of both agencies he was able to prevent the precipitation of the relatively insoluble electrolytes of calcium and phosphorus, which participate in the formation of calcium and phosphate stones. This reaction takes place regardless of diet or infection of the kidney.

The doubtful efficacy and limitations of dietary and medicinal agents to dissolve or prevent stone formation led Suby and Albright (7) to investigate the effects of citric acid sodium citrate solution in the dissolution of stone. They found this solution would destroy the mucous membrane of the bladder in a short time, but they also found that by the addition of magnesium oxide, they lost none of the dissolving properties of the citric acid solution and the irritating effects of it on the bladder mucuosa were neutralized. This resulted in a buffered citric acid solution which is known as G solution and is particularly efficacious in dissolving loosely constructed calcium and phosphatic stones by means of direct application of the solution to the stone.

Another interesting if not so practical application of medicinal agents in the dissolution of urinary incrustations is furnished from the fact that in the waters of the Amazon Basin is a little fish (Candiru) which penetrates the urethas of men and women bathers particularly if they should pass urine when in the water. The great speed of this little fish allows it to enter the urethra and bladder as the urine is being expelled. Here it attaches itself to the mucuosa of the bladder and produces a very painful lesion. The natives have found that by making a brew of the Buitach Apple (*Genipa americana*) which grows in the Amazon Basin and when drunk very hot has the property of dissolving the skeleton of the fish. This has resulted in an analysis of the brew and its application for the dissolution of bladder incrustations due to calcium salts. A synthetic formula of this brew has been composed and used with success by Dr. Lin (8) in cases of encrusted bladder. The formula is administered by means of rectal injections.

In 1941 Huggins (9) advocated bilateral orchidectomy for carcinoma of the prostate and later introduced stilbestrol in the treatment of the same condition. Both procedures have proved to be immensely valuable and represent progress in the treatment of carcinoma. During the last five years urologists have tried to determine the efficacy of each procedure. After the diagnosis of carcinoma of the prostate has been established, the following questions always arise: (1) When should we do orchidectomy; as soon as the disease is diagnosed or should it be reserved for patients with marked metastases, pain and other symptoms? (2) Should stilbestrol be used first to be followed by orchidectomy late in the disease? (3) Should orchidectomy be performed first followed by the use of stilbestrol or (4) should one method be used to the exclusion of the other? During the last five years physicians have had enough experience with both procedures to render opinions and their value. To determine the trend of clinical opinion, Meads (10) recently sent out 100 questionnaires to urologists concerning the above questions. Out of 78 replies, 70 urologists favored orchidectomy. . . . Of these 23 insisted the operation should be done early and 47 were convinced that it should be performed late, that is, when signs of metastases had developed as evidenced by pain, x-ray findings and rise in serum acid phosphatase.

Huggins wrote: "We still believe that bilateral orchidectomy is considerably superior to estrogenic treatment, feeling that the remission is greater and more prolonged. Further, we do not give patients who have had orchidectomy estogen except occasionally for a short period of relieve hot flashes. Our preference for orchidectomy over estrogenic treatment is not one of caprice, I believe, since we had the pleasure of introducing both methods of treatment for this disease. We proceed with the removal of the testes as soon as the diagnosis has been made, except that an occasional patient is encountered with a lesion small enough for radical perineal prostatectomy. Incidentally, in Chicago this happens once in a blue moon."

Forty-seven urologists believed that stilbestrol should be administered first and bilateral orchidectomy delayed until late in the treatment of carcinoma of the prostate. Young believes that if it is a carcinoma entirely confined to the prostate, radical operation may cure; if it is too extensive for radical operation, stilbestrol in doses of five milligrams daily. When stilbestrol fails, orchidectomy is certainly indicated. Braasch (3) says we reserve orchidectomy until metastases and severe pain develops. Nesbitt reserves orchidectomy for patients who show evidence of an advanced disease.

Mead's paper shows that about one-third of the urologists perform bilateral orchidectomy for carcinoma of the prostate as soon as the diagnosis is made, and that two-thirds delay this operation until metastases can be recognized. While this paper represents nothing new, it does summarize the trend in application of a very valuable procedure in prostate carcinoma.

A new way to apply x-ray therapy to bladder tumors has been advanced by Rose (11). He believes that carcinoma of the bladder of the invasive type is sufficiently similar to skin cancer and if direct x-ray exposure could be successfully applied in the bladder as in the case of skin cancer, we might hope to cure certain carcinomas of the bladder by this method. To apply x-ray in this manner he opens the bladder widely to expose the tumor and by means of a sterile lead shield the x-ray is applied directly through the wound. He anticipates favorable results in about 25% of the cases and believes the procedure is another aid to be considered in bladder malignancies and states that his ten years results are very promising.

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RECENT ADVANCES IN OPHTHALMOLOGY

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Prior to the present war, research in the field of plastics was advancing into new fields. New varieties of plastics and new uses for them have been found. Thus in the field of ophthalmology we have parts of optical and surgical instruments being made of plastic. There is a transparent retractor of plastic, useful in the retinal detachment operation. Sets of prisms used for measuring muscle imbalance are available but have the objectional feature of being more easily scratched if subjected to hard usage. We have heard much of the prosthesis or "glass eye" made of plastic. It is true that a much better prosthesis can be made of plastic than those we have had before. A mold or pattern can be made of the socket, a plastic casting can be made from this mold which will fit that patient. It is non-breakable and can be repolished when it becomes rough, whereas a prosthesis made of glass must be replaced after a few years because it becomes discolored and rough. It has long been recognized that even the best fitted prosthesis has its limitations. Since it fits by contact under the lids, its motion is limited. This is true particularly in the horizontal plane where its movement is limited by the bony orbit. The correction of this obvious defect has baffled eye surgeons for a long time. At present there are several operations being developed to overcome this objection. One such operation may be briefly described as follows: The enucleated eye is replaced by a complete plastic eye, the posterior half of which is covered with a tantalium wire mesh. Small tantalium plates are sutured to the four recti muscles. These plates are then properly attached to the prosthesis. Such technique permits complete freedom of motion of the prosthesis. As is usually the case certain technical improvements must still be made before this operation can replace the older method. Contact lenses are now being made of plastic, therefore less dangerous to the wearer than those made of glass. Contact lenses of glass are not new, having been originally devised for persons suffering from conical cornea. It might be mentioned here that contact lenses have very definite indications for their use and in no sense are to be regarded as a substitute for glasses.

The coating of optical lenses with a substance to eliminate annoying reflections is making progress. When first developed it was discovered that the coating could be wiped or washed off when cleaning the lens. It is believed that this objectionable feature is not yet ready for the market in any quantity.

A simple device was produced to assist in localizing intraocular foreign bodies. It consisted of a plastic contact lens with four equidistant metalic dots in it so arranged that these dots were very close to, or in contact with the limbus. Military hospitals where the removal of intraocular foreign bodies was being done found that the information obtained by this localizer was often very valuable.

Improvement has been made in the operation for transplantation of the cornea. More eye surgeons are performing the operation, and as instruments become available we can expect this relatively new surgical procedure to become more common. An eye bank has been established in New York City to which donors eyes may be sent. It has been found that the cornea of such eyes sent to the eye bank are suitable for transplantation 36 to 48 hours after leaving the donor. Enucleated eyes with normal cornea should not be wasted. There is a waiting list of those who need them.

Experience gained in the war has given us a much better understanding of the indications, limitations and use of penicillin. Detailed information is now available in current literature. One example may be cited. In Ohio it has halved the taxpayers cost for the care of gonorrheal conjunctivitis in the indigent, and concurrently visual loss from the same cause has been greatly reduced.

RECENT ADVANCES IN PEDIATRICS

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The time allotted could be spent entirely in merely cataloguing the many recent advances in Pediatrics. Instead of this, I would prefer to discuss in some detail two of the concepts which have grown to prominence recently which appear to be of fundamental importance.

CONGENITAL ANOMALIES FOLLOWING GERMAN MEASLES IN THE PREGNANT MOTHER

Until the past few years it has been generally accepted that congenital malformations result from defects in germ plasm existent prior to conception. A very significant advance in thinking concerning the etiology and prevention of such anomalies has followed the demonstration that maternal infection may also play a part in their origin. Following an epidemic of German Measles in Australia, Gregg (1) noted what seemed to him to be a veritable epidemic of babies born with eye and heart anomalies. Further study revealed that most of these particular babies had been born of mothers who had had rubella during their pregnancy. Swan (2), also in Australia, soon corroborated these observations and extended them to include pathologic reports of three such infants who died of intercurrent infections. At least five American authors have also found similar cases in their experience (3). To the present, these workers have reported 145 instances of various congenital anomalies in mothers with a history of rubella during pregnancy. In 77 of these, the anomalies were multiple. Mental deficiency was seen in 88 cases, cataracts in 112 cases, heart malformations in 83 cases, microphthalmos in 13 cases, and deaf mutism in 12 cases. It seems inconceivable that such a number of malformations should be brought to light in the few mothers that wait until pregnant to develop this childhood disease.

It is obvious that attention has been called to this relation because of the malformations rather than the maternal rubella. However, it is difficult to collect accurate statistics on the total number of mothers who have rubella during pregnancy and subsequently compare their offspring with a control series as to the incidence of anomalies. There might be considerable doubt concerning the validity of the above relationship if it were not for another observation too unique to be due to coincidence. With the exception of four cases, all the 145 mothers had their rubella before the fourth month of pregnancy. Swan reported observations on 49 cases of rubella in all stages of pregnancy of which 25 occurred before the third month. Every one of these infants was malformed. Four out of eight infants whose mothers had their disease in the third month were malformed, while beyond the third month, only two out of sixteen showed defects. This fact has led to speculation that the fetal infection which is assumed to occur must affect the fetus during a stage of critical development of the eye and heart structures for an anomaly to result.

These results have stimulated several investigators to explore the possibility of other maternal infectious diseases leaving deformed offsprings in their wake. This search has so far been rather fruitless since only two cases have been found in which the mother had mumps, and two in which she had influenza. Apparently German Measles is not as innocuous as was once thought. These observations and similar ones of his own have led Erickson to suggest mandatory abortion of any mother acquiring the disease in the first trimester of pregnancy.

CYSTIC FIBROSIS OF THE PANCREAS

Anderson (4), and Blackfan and May (5) independently in 1938 described a syndrome in infants resembling celiac disease in some respects which has come to

be known as cystic fibrosis of the pancreas. This is not a particularly rare disease, for we see four to six cases a year at Children's Hospital. Attention was directed to the condition by the observation that some children with celiac syndrome eventually recovered, while others suffered repeated and severe pulmonary infections which were invariably fatal. According to the concept developed by Farber, the condition is an hereditary one. Sometimes at birth and other times during the first year, the secretion of the pancreas becomes so thick and viscid as to effectively plug the secretory ducts and stop the flow of pancreatic juice. This deprives the bowel of pancreatic enzymes and leads to a fatty diarrhea. As the result of the plugging of the ducts, the acini become grossly dilated and cystic, and the pancreas undergoes fibrosis. This picture of pancreatic involvement is striking and constant. However, many other glands in the body may also undergo the same alteration in secretory power. The bronchial mucus glands are often involved, resulting in the secretion of a substance so thick and tenacious that it cannot be effectively removed from the bronchial tree. Infection with low grade pathogens from the pharynx (Staphylococcus aureus usually) then takes place following an upper respiratory infection. The pneumonia is characterized by marked emphysema from the air trapped behind the sticky plugs of mucus. Clinically, these patients are usually thought to have whooping cough at first, so violent are their attempts to clear their air passages. The salivary glands, lachrymal glands, Brunner's glands, and even the liver have in some cases been the site of the same unphysiologically thickened secretion.

The pancreatic deficiency causes a loss of excess fat and protein in the stool, so that these children may be quite malnourished though possessed of an exceptionally good appetite. Even more important is the aspect of pulmonary infection which, once it becomes established, is with rare exceptions fatal in the end.

The diagnosis is complicated by the insidiousness of the onset. In most of the cases, the true nature of the condition has been first found at autopsy. Recently, however, it has been recognized during life by suspecting the condition in any infant with so-called whooping cough, or chronic pneumonia, or repeated bronchitis whether or not the child also shows evidence of steatorrhea. Thus, clinically, although the disease is still called cystic fibrosis of the pancreas, most diagnoses during life are made by attention to the pulmonary symptoms.

The true nature of the condition is established by demonstrating the absence of the enzyme trypsin in the pancreatic juice. This is accomplished by sampling the contents of the duodenum in the fasting state by means of a Levine tube. Dilutions of the duodenal juice are then allowed to act on gelatine. If the gelatine is not liquified, it is taken as evidence of an absence of trypsin. The procedure is more difficult than it sounds since it is a long and arduous one, especially in a child who is dyspneic from his pulmonary involvement. Any contamination of the duodenal juice with stomach acid may invalidate the test, and sometimes it is practically impossible to enter the duodenum with the Levine tube.

Recently, West and Wilson have proposed an equally logical test based on the observation that these children cannot break down proteins sufficiently into their ultimate amino acid components. A test meal of casein or gelatine is given after a fasting determination of the blood amino acid content. Thereafter, in the manner of a glucose tolerance test, serial amino acid "levels" are taken. Normally the fasting value is close to 1 mg. %. In the normal infant this rises to 4 or 6 mg. % after a casein meal. In cystic fibrosis of the pancreas, there is no significent rise.

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SOME RECENT ADVANCES IN PHYSIOLOGICAL CHEMISTRY AND NUTRITION

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It is a most difficult task to attempt such a brief review of recent advances in physiological chemistry and nutrition. Last year (1945), even after a succession of war years, 8,137 abstracts on biochemical subjects appeared in *Chemical Abstracts* in the Sections on Biochemistry and Foods alone. Also, we have the further evidence of the tremendous activity in this field in the appearance each year of the *Annual Review of Biochemistry*, the most recent volume of which (for 1944) comprised 856 pages. Accordingly, the material presented here will be quite general and will be illustrative of trends of development over the past few years rather than an attempt to cover any field in detail.

The Carbohydrates.

The three most important polysaccharides in nature are cellulose, starch and glycogen. The structures of these compounds are similar in that they are made up of glucose units bound together between the 1-C of one glucose molecule and the 4-C in the next. The view that this 1–4-linkage is the one always elaborated by natural synthesis has been contradicted in recent years by the discovery of carbohydrates with 1–2-, 1–3-, and 1–6-linkages. Starch is believed to be a molecule made up of *repeating units*, each consisting of from 24 to 30 glucose molecules (1), and combined by cross linkages to form a molecule of about 200,000 molecular weight. Most natural starches contain at least two components, designated as amylose and amylopectin. Thus, corn starch (2, 3) contains 10–20 per cent of amylose of unbranched chains of molecular weight 10,000 to 60,000 and 80–90 per cent of amylopectin with highly branched chains of 50,000–1,000,000 molecular weight. The most important polysaccharide in the human body is glycogen, the molecule of which is considered to be spherical in shape and to which a weight as high as 4,000,000 has been assigned (4). Such a molecule would contain nearly 23,000 glucose units.

The role of phosphoric acid in nearly all of the phases of carbohydrate metabolism has now been well established, beginning with the phosphorylation of absorption and ending with its various functions in the utilization of carbohydrates in the tissues. A most interesting achievement is that of Green and Cori (5) who isolated phosphorylase from rabbit muscle. One of the components of this enzyme is a crystalline euglobulin of molecular weight 400,000. This enzyme catalyses the formation of glycogen from glucose-1-PO_4, and presumably also the breakdown of glycogen. By studies with deuterium labelled compounds Stetten and Boxer (6) showed that 69 per cent of liver glycogen (in rats) was turned over daily but only 19 per cent of carcass glycogen. Labelled CO_2 has been shown to appear in both liver and heart muscle glycogens (7). The course of intermediary metabolism of carbohydrate, leading to its final oxidation, is still the subject of active research and rapidly changing views with practically no final answers to the problems raised. In this connection the Krebs tricarboxyllic acid cycle is most often mentioned (8).

The Fats and Oils and Other Lipids.

Methods for studying the glyceride structure of the fats and oils and of their component fatty acids are being continually improved. It is now possible to evaluate the fatty acids of these lipids with a high degree of accuracy, and in many

instances to discover new fatty acids, hitherto not believed to be present. Thus, a few years ago hexadecenoic acid was a rare compound in fat chemistry. Now, as a result of refinement in distillation and other procedures (9) it has been found in most animal fats examined, including human fat (10) and human milk fat (11), the latter containing 2.6 per cent of this acid.

The separation of fatty acid mixtures by low temperature crystallization from organic solvents (12) and the development of spectrophotometric procedures for the estimation of unsaturated acids with more than one double bond have proved to be important methods of study. Several reports have already noted the occurrence of fatty acids with conjugated unsaturation in naturally occurring lipids. The significance of these compounds in fat metabolism has not been studied.

More and more attention is being paid to the lipo-proteins (13). The lipid components of these compounds are usually not extractable from tissues without being previously diassociated from the proteins by hydrolysis (HCl), by extraction with methanol or ethanol, or by such a mild treatment as freezing at —25° (14), this last treatment having been shown to release the bound lipids of blood plasma.

An interesting development in fat metabolism is the view expressed by Frazer (15) that glycerides can be absorbed as such. Thus the classic concept of the necessity of complete digestion to fatty acids and glycerol preliminary to their absorption seems to be seriously questioned. Depancreatized dogs absorb up to 75 per cent of ingested fat (16). Other developments in fat metabolism have been due in no small part to the use of tagged molecules, especially the deuterium, used first by Schoenheimer and coworkers (17). Thus, the processes of desaturation of fatty acids, of interconversion of one fatty acid with another in the tissues, and of new functions of depot fat have been experimentally demonstrated. The fat depots seem to be one of the important destinations of dietary fatty acids, even when they are fed to a partly starved animal. Depot fat, long considered to be an inert storage material, has now assumed the role of a rapidly changing, functioning organ. In fact, the half-life periods of the fatty acids of various tissues have been actually determined (18, 19). Likewise, we are seeing rapid changes in the theories of fat utilization. The classic beta-oxidation theory is now scarcely recognizable, although it still accounts for a considerable part of the oxidation mechanism. The production of ketones is considered to be a normal process, largely resulting from recombination of the acetate residues or "active acetyls" produced by beta-oxidation. Incidentally it has been suggested that acetoacetate, or some other similar product of fat metabolism, enters the scheme of carbohydrate metabolism by conversion to oxaloacetic acid which is one of the compounds of the citric acid cycle (20). In this sense fat and carbohydrate metabolism merge into each other, and the fat does indeed burn in the flame of the carbohydrate, as we were teaching twenty years ago.

The Proteins.

Two recent volumes on "Recent Advances in Protein Chemistry" have reviewed progress in this field (13). All crystalline enzymes so far isolated have been found to be proteins. In the pituitary gland alone at least six hormones of a protein nature have been demonstrated and their properties described. In the later aspects of this work the Tiselius electrophorometer has been especially useful, as well as in extensive work on the patterns of the plasma proteins. The plasma proteins have been the subject of a most extraordinary series of fractionations by the Harvard group, headed by E. J. Cohn (21). From human plasma several simplified protein fractions have been prepared, studied, and adapted to specific uses in medicine. Thus, the gamma-globulins possess an antibody titer approximately ten times that of pooled plasma and can be used to confer passive immunity against measles, infectious hepatitis, and the like. Albumin of over 98 per cent purity is available in 25 per cent solution for use against shock and for many other purposes.

Incidentally, the albumins and globulins are heterogeneous in composition, and are usually associated with lipid and with glucosamine,—thus in fact being conjugate proteins. The viruses, which are found in the border zone between bacteria and non-living protein molecules, have been shown to be nucleoproteins of very high molecular weight and to possess the unique property of reproduction.

Study of protein metabolism with isotopic N^{15} has demonstrated the rapid interchange between dietary nitrogen and the nitrogen of the amino acids in the protein molecule of the living tissue; this isotope has also been employed in studying the intermediary metabolism of the individual amino acids. By this method, creatine has been shown to be derived from three sources, glycine, arginine and methionine, each of these amino acids contributing specific fragments to the creatine molecule.

Hydrolysates of complete proteins such as casein and lactalbumin are coming into use in medicine in the treatment of hypoproteinemia and other disorders; some of them are suitable for parenteral administration. According to the newer views the plasma proteins are in dynamic equilibrium with the proteins of the tissues. Theoretically, at least, the total protein nutrition of an individual can be adequately supported by administration of the plasma proteins.

General Trends in Nutrition.

The last ten years of research in nutrition have seen the field develop from a qualitative to a fairly quantitative science. Most of the better known vitamins have been identified chemically, many of them are prepared synthetically so that they are very inexpensive, and accurate methods for their quantitative estimation have become available. We now have accurate tables of analysis of the several vitamins, which suffice for many nutrition studies without actual food analyses. From such data it has been possible to evaluate quantitatively the diets of population groups and to compare their dietary habits with the standard requirements.

In the two or three years before the war our government became nutrition conscious as a consequence of many of these population studies, as a result of which the Surgeon General came out with the statement that nearly half of the American people were living on diets which were deficient in one or more items. The committee on Foods of the National Research Council was formed, one of its important contributions being to set up a list of recommended dietary allowances which have served as standards during the war both for this country and others. This has been a powerful influence toward better nutrition throughout the world, although the present food shortages are working in the other direction. The recommended allowances may be higher than necessary in some instances, as subsequent work is now showing.

It is true that deficiencies of clinical severity are rare in this country, but there is adequate evidence that pre-clinical inadequacies are relatively common. Incidentally the exigencies of war and its concurrent incidence of severe starvation of peoples in the occupied nations and in prison and concentration camps have for the first time given many of our doctors first hand experiences with the classic diseases of nutrition.

A great deal of important work relative to the vitamins during the past few years has been concerned with the further study and isolation of the lesser items of the vitamin B-complex, as for example, folic acid, pantothenic acid, choline and numerous others. The recent finding that folic acid will cause remission of certain types of anemia and the importance of choline in preventing fatty liver are examples of developments in this direction which have proved to be of use in medicine. Most of these newer B-complex vitamins have not as yet been applied to human nutrition, and undoubtedly research in the near future will add most interesting chapters to the story of this science.

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RECENT DEVELOPMENTS IN THE FIELD OF HEMATOLOGY.

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Progress in both the fundamental and clinical phases of hematology during recent years has been phenomenal. The complexity of bone marrow has been greatly simplified, and the mystery, which for so many decades, surrounded the spleen has become less enigmatic. Both spleen and marrow bear an intimate relationship to each other, and, in turn, to the vital economy of the body as a whole. In the detailed knowledge now available, we have the key to the solution of a whole host of human diseases, some hitherto unrecognized, and, therefore, uncontrolled. Moreover, some of the basic mechanisms are now revealed, whereby new syndromes or combinations of disease syndromes may be detected early, and direct rational measures of control instituted promptly with confidence and with dramatic clinical results.

The most recent significant clinical application of basic information, accumulated from a wide variety of sources through the past ten years of intensive chemical and biological investigations, is that involving so-called folic acid, a derivative of the vitamin B complex. There are five designations which have been somewhat indiscriminately applied to this "group" of compounds: vitamin Bc (essential to growth and hemoglobinogenesis in young chicks), vitamin M (essential to hematopoiesis in monkeys), Lactobacillus casei factor (essential to the growth of these milk-souring bacteria), folic acid (derived from the "foliage" of spinach), and eluate factor (chemical procedure in processing liver, yeast and other natural sources). A conjugate of B_c has been isolated from yeast, having a more complex molecular structure 2.8 times that of the simpler B_c obtained originally from liver. Typical vitamin B_c may be obtained from the "conjugate" on enzyme digestion.

The culminating climax of these fascinating studies came last August (1945) with the announcement by Angier and associates of the chemical synthesis of a compound, recently revealed as pteroylglutamic acid, and ultraviolet and infrared absorption spectra, crystalline structure and *biologic activity* identical with L. casei factor isolated in pure form from liver by Stoksted and Manning (1938). The importance of this discovery cannot well be overemphasized or overstated. The "yield" of this biologically essential molecule from natural sources, such as liver, is exceedingly small, 0.1 ounce from one ton of beef liver, so that to have it available in relatively unlimited quantities the synthetic chemist has immeasureably enhanced its effective application both clinically and in further biologic exploration.

Studies in this field were begun in this laboratory in 1940, with Drs. Woolpert, Henry Wilson, Samuel Saslaw and associates in the Department of Medicine and Bacteriology. Rhesus monkeys were used on experimental dietary regimes and it was determined that without "folic acid-containing concentrates" a gradual pan-marrow hypoplasia developed. Langston and associates had previously shown that diets of the Goldberger, black-tongue type were inadequate, and that liver or yeast contained a common essential for normal hematopoiesis in the monkey, "vitamin M." Granulocytopenia occurred in 100 per cent of our dietary deficient monkeys, anemia in approximately 50 per cent. Folic acid concentrate was found to be invariably effective in relieving the granulocytopenia at once, within 24 hours, in our monkeys, and, in those animals showing also anemia, a reticulocyte response was elicited followed by red cell and hemoglobin regeneration entirely comparable to the anti-anemic response to liver extract. Blood thrombocytes also returned to normal.

The translation and transferage of the animal results to clinical patients was begun in the summer of 1943 in Birmingham, Alabama, in association with Dr. Tom Spies. Patients chronically deficient in many dietary essentials, more particularly the vitamin B complex, were selected, who showed clinically, frequently recurring oral ulcers, associated with a leucopenia hematologically. Folic acid was then given under controlled conditions, and both clinical and hematologic improvement was noted. Later the synthetic molecule was substituted for the natural source with similar results.

With the availability of larger quantities of synthetic folic acid (pteroylglutamic acid) in the early fall of 1945, Spies extended the use of this material to the macrocytic anemias in and around Birmingham with spectacular responses. Darby and Jones reported from Nashville the response of macrocytic anemia in non-tropical spure, and Moore and associates in St. Louis and our own group here, comprising Henry Wilson and Claude Starr Wright, found equally spectacular results in Addisonian pernicious anemia and the macrocytic anemia of pregnancy. Spies then showed that the macrocytic anemia of tropical sprue in Cuba responds promptly. Furthermore, it has been established that those patients sensitive to liver and liver extract may receive folic acid synthetic with impunity and with the maintenance of complete clinical and hematologic remissions. It remains to be proved whether the neurological changes, associated with pernicious anemia in many patients, will remain permanently under control with folic acid.

There is good reason to believe at the present time that pteroylglutamic acid is not the active principle in liver nor is it the extrinsic factor of Castle. The exact and precise role of this extremely interesting and important molecule in the complex chemistry of hematopoiesis remains to be determined, but a new and fascinating chapter is being written in fundamental biological mechanisms and a new and potent therapeutic agent has been made available for the relief of a large number of human sufferers.

THE PRESENT STATUS OF ALLERGY IN CLINICAL MEDICINE

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Allergy in its various forms has been known for ages, but in recent years it has taken on a new importance. A knowledge of its management is even more important now that we know so much more about the condition. Moreover, industrialization and the consequent centralization of 85 per cent of our population seems to have made all allergic manifestations more prevalent. Our attempts to control our climate by means of air conditioning machines are still crude. They merely add to the wide variations in temperature and humidity to which we are already subjected. These variations in our environment produced by modern living put a great strain upon our autonomic nervous systems. As the years go by more and more of us develop imbalances of the nervous system which increase our disposition to develop allergy.

I make mention of this important fact because the students of the new school of psycho-somatic medicine regard the whole field of Allergy with a possessive eye. They point to the fact that a great percentage of psycho-neurotics are also allergic. To support this conception the age-old story is told over and over again of the woman who was allergic to roses and who on one occasion was seized with sneezing when a vase of paper roses was brought into the room. We all recognize that our mental reactions are the function of our brains. Emotional upsets are likely to bring on an allergic attack or to make it more severe than it otherwise would be only to the extent that they disturb the physiology of the individual. Stoic Indians, cows, and dogs are victims of Allergy just as are psycho-neurotics. So it would not seem wise to turn the field of Allergy over to Psychosomatic Medicine.

While Allergy has come to be a great joke in the radio world, we in the medical world do not take it so lightly. It has been found to be a cause of asthma, hay fever, sinus disease, hives, ango-neurotic edema, eczema, dermatitis, migraine headaches, colitis, epileptoform seizures, high blood pressure, and various disorders of the heart and other organs.

The commonest manifestations of Allergy is, of course, hay fever—properly called timothy allergy in its May and June phase and ragweed Allergy in late August and early September.

In reading the modern literature on Allergy one is thrown into great confusion. The reason for this is that there is a strange misuse of terms. To understand clearly even the popular literature on the subject one must realize that there are several types of Allergy. In the presence of all available knowledge we should recognize the following different types: (1) atopic; (2) non-atopic. Under this last we put: non-reagenic familial Allergy; the Allergy of infection; Allergy to chemicals, including contact Allergy; Allergy to serums; Allergy to physical agents.

The name atopy (literally a "strange malady") was given by Coca to the common Allergy of the ordinary case of hay fever, asthma, hives, and eczema to distinguish it from reactions to serums, ivy and primrose poisoning, and the hypersensitive reactions of tissues to the tubercle bacillus. Coca emphasized that it was a disease limited to human beings, that it was apparently inherited, and finally that it was characterized by the presence in the blood and tissues of its victims of a special kind of antibodies which he called *reagins*. It was later shown that these reagins were transferable to normal individuals. Strangely enough what literally thousands of farm people knew, namely, that dogs, horses and cows can and do suffer from atopic manifestations did not get into medical literature for a good many years.

The idea that atopy is inherited along Mendelian lines may be true. The familial appearance, on the other hand, may mean only that the genes have been

affected in some way by weather, nutrition, or other environmental factors. At any rate the concept of inheritance breeds despair when exhibited in our consultation rooms. Those among us physicians who are of an academic turn of mind cause much needless worry by invoking eugenics. As the late Logan Clendenning rightly observed: "Men are not going to embrace eugenics, they are going to embrace the first likely trim-figured girl with limpid eyes and flashing teeth who comes along in spite of the fact that her germ plasm is probably reeking with hay fever."

It is the third remaining characteristic of atopy named by Coca that constitutes the backbone of the modern treatment of Allergy. This characteristic is the presence of antibodies which may be detected by skin testing and which can be transferred in the serum of the patient to the skin of another individual. This characteristic is generally recognized now and made use of in the search for the cause of the particular allergic manifestation under investigation.

In recent years, Coca has described cases of familial migraine, urticaria, coryza, and asthma in which no reagins could be demonstrated. And which apparently did not fall into the regular types of non-atopic Allergy. In those suffering from this disorder Coca has found disturbances of autonomic nervous system in which the offending allergens could be detected by the marked increase in pulse rate which their presence induced. He reported that severance of the sympathetic nerves gives complete and permanent relief.

Although Coca's concept and its interpretation have not been investigated as thoroughly by others as they deserve, they do illustrate that neuroses, organ neurosis, and shock are matters of degree, and that the clinical manifestation represents Nature's attempt to prevent the break-down of a personality.

An Allergy to chemicals accounts for many cases. It consumes a large portion of the workmen's compensation funds earmarked for occupational diseases. Not much has been said in the literature about the possibility of contact other than in plant dermatitis and occupational dermatoses, but certainly most allergists are familiar with cases of coryza and asthma which have been induced through a specific hyper-sensitiveness to oils, fumes and gases. Some years ago I expressed the opinion that these were due to a contact Allergy—an opinion which others more recently confirmed. Many drugs, especially the organic ones, act as allergens. For years aspirin has been the worst offender and the most difficult to manage. But now it is being shoved aside by sulfa-drugs and penicillin. The mechanism has been quite clearly defined by Landsteiner, who has shown that the chemical unites with the serum of the victim to form a conjugate that can then act as a protein allergen. From this point on, the story of each case is exactly like that of serum sickness.

The most common reaction to penicillin is urticaria. This occurs in 5 per cent or more individuals who are undergoing systemic treatment. Vesicular eruptions occasionally occur and they resemble dermatophytids. Penicillin has provoked exfoliative dermatitis.

The allergy of infection is important. Some authorities question its existence. This again is pretty much a matter of terms. The usual definition of Allergy is that it is an abnormal and harmful response to a substance which is not harmful to normal individuals. This is a perfectly good definition of atopen, but it cannot be made to apply to the hypersensitiveness that develops in our bodies toward bacteria with which we have had an encounter. In fact, the severity of our illness during the course of an infection is an expression of this form of Allergy. Upon this fact depends the use of skin testing for the recognition of tuberculosis and undulant fever. There can be no doubt that hypersensitiveness or Allergy, if you will, to bacteria, is a very real thing.

Then there are people who will develop all of the signs and symptoms of one of the allergic manifestations when they are exposed to cold, or heat, or light, as the case may be. These conditions have been named by Duke as physical Allergy.

Compared with them, however, are other members of which heat, light and cold only serve as precipitating factors on account of the nervous imbalance. These and many other accessory factors predisposing at times to an attack of Allergy have at some time been brought forward as the cause of the condition. Among such secondary factors are: barometric changes; temperature changes, especially cold; light; emotional upsets and worries; fatigue; focal infection; acute and chronic infections; constipation, especially with food allergy; deficiency states such as malnutrition, hypochlorhydria; vitamin deficiencies, and particularly thyroid and liver disfunction; and mechanical and chemical irritations, especially dust, dirt, gases, fumes, or fogs.

Skin testing is a convenience when properly performed, and often saves time for the patient. It must be remembered that skin tests do not indicate for certain that the test substance is or is not the cause of his trouble. They are merely clues, the significance of which depends upon the knowledge and skill of the physician and above all upon his familiarity with the properties of his own testing material. For this reason every allergist wants to do his own skin tests in his own way with his own materials. It cannot therefore be emphasized too strongly that skin tests with atopens are only clues to aid and facilitate the search for the real offenders. Good medicine can be practiced without them if necessary.

Like certain other biological phenomena used in medical diagnosis, skin tests require interpretation, because positive reactions may be persisted from previous allergic disturbances, even in other parts of the body. These reactions—for example, pyloric stenosis, infantile eczema, or cyclic vomiting in children—may or may not have been recognized as allergic manifestations at the time of their occurrence. The most common of such reactions is a positive reaction to ragweed or timothy pollen after one season before the initial onset of hay fever in the next season. Finally, at times certain testing materials may be irritating in themselves and so give false positive tests on everyone, or they may become irritating if not properly kept. Extract of house dust, silk, tobacco and certain foods such ns rhubarb and cranberries have to be watched closely in this respect.

All substances that are suspected should be put to clinical trial under controlled conditions, regardless of the results of the skin tests. Likewise, all positive tests must be proved before they are accepted. We see all too many patients who may or may not be allergic to certain substances but who think that they are because they have been told the skin tests to those substances were positive. Too frequently also we hear that the patient was tested and was allergic to nearly everything. It is the rule to be allergic to one or two inhalants and a food or two and possibly a pollen or two but seldom any more.

Treatment.—So far as the relief from the torments of allergy are concerned the greatest advance was made when we were given epinephrin for hypodermic injection. Then came ephedrine with like action but with the advantage that it could be given by mouth. In recent years, the sufferer from severe asthma has been blessed by the introduction of aminophyllin and more recently by its administration in rectal suppositories.

I, with certain others, began the use of histamine some 16 years ago. We found that by frequent injections of carefully graduated doses of very small amounts of histamine we could obtain relief in hives and certain forms of headache with surprising regularity. Then came attempts to tie histamine to some chemical so that it would be gradually released to the body for the purpose of stimulating the body of the allergic to produce enough of the anti-histamine enzyme to destroy at once the histamine released by the struggle between the allergen and its antibodies. In the meantime, the isolation of the enzyme, Histaminase, gave great promise but failed us when put to clinical trial. So the investigators went back to conjugating histamine with various chemicals. The first to be given extensive trial was Hepamine—a conjugate with an azoprotein from horse serum. The

Committee of Treatment of the American Academy of Allergy issued just yesterday its pronouncement that histaminase (Torantil) and Hepamine are of no value in the treatment of allergic diseases. Benadryl holds the stage at present.

Benadryl.—It is supposed that in anaphylactic shock in animals and in the allergic phenomena of human beings there is released a histamine-like substance which accounts for the clinical signs and symptoms. Various anti-histamine substances have been developed, some of them too toxic for general use, but one will hear a good deal of a recently developed benzhydryl compound which has been termed benadryl. When administered orally in doses of 50 to 100 mg. three to five times daily, it is highly efficient in controlling symptoms of acute and chronic urticaria and angioneurotic edema, although the relief is purely palliative. Side effects are not serious: drowsiness, dizziness, dryness of the mouth and dilated pupils may be noted. The drug is given by mouth or by the intravenous or intramuscular route. Preliminary investigations indicate that benadryl relieves pruritus in certain dermatologic conditions besides urticaria; therefore, extensive use of the drug may be anticipated. In my own experience it is a complete disappointment. It only confuses and delays the systematic investigation of hives.

One other drug needs to be mentioned to be condemned and that is ethylene disulphonate. As the Director-General and Editor of *The Letters* of the International Corespondence Club of Allergy, this has caused me no end of trouble. Appearing into respectable circles with a shadowy background, ethylene disulphonate was hailed by the daily press and *Time* magazine as "the one-shot cure" for allergy. It had a great run in Australia at 75 dollars an injection. It lived for awhile in scientific circles in England. In the United States some half a dozen honest men believed that they got good results with it. Careful trial at the University of Maryland and at the University of Minnesota have shown that it has all of the properties of triple distilled water. This left two questions: Are the chemicals which act as reduction enzymes in dilution so great as not to be detectable by ordinary chemical analytical methods, and secondly, what does happen when you give an intramuscular injection of distilled water? Is any histamine-like substance released? These questions appear to me as important, but are being used here as a defense to hold the line while many more vials of the one shot cure can be foisted upon the American physician anxious to give his allergic patient the benefit of the latest thing.

In conclusion, may I warn you against getting lost in the semantics of allergy. Remember that there are seven different kinds. Please be advised that none of the new remedies are much good but that the tedious treatment with pollen and other protein extracts brings about complete and permanent relief in better than 50 per cent of cases and relief in all but a few, that asthma can be controlled and that all forms of hives respond promptly to systematic management and investigation. We in allergy are proud of the clinical results that we get for they are much better than the average in clinical medicine.

We look forward with you to the day when the missing factor whose absence makes a Don Quixote of the tissues of the allergic so that they go off tilting at windmills will be found but in the meantime there is no reason for the allergic to be in any way discouraged.

RECENT ADVANCES IN NEUROLOGY AND PSYCHIATRY

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The last few years have witnessed notable advances in the fields of Neurology and Psychiatry. World War II has served as a vast experimental laboratory in these areas. Modern explosives and present day combat conditions resulted in a large number of brain injuries, some of which were the "open type" of head injury with exposure and laceration of the brain, but a larger number were of the "closed type" of head injury in which the brain is damaged but not exposed. In the field of psychiatry, World War II made it possible to evaluate the psychiatric status of between ten and fifteen millions of Americans who were supposedly in the prime of life. The amazingly large number of these who were found unacceptable for military duty was one of the most alarming pieces of information to come out of the war. Those who were taken into military life were subjected to the rigors of that abnormal existence, and in the process many thousands broke under the strain. It is now well agreed that the major factor in those breakdowns was the conditioning of the personality before induction into military service rather than the actual war experiences, terrible though they may have been.

The large number of neuro-surgical cases that were seen in the War has resulted in many improvements in technique and management. One of these is the use of the substance, fibrin, in neuro-surgery both as a "glue" for severed nerves and in the form of sheets to cover the brain after it has been exposed by injury or after operation. The use of the metal, tantalum, in the repair of nerves and to fill in skull defects is becoming well known. The tissues react much less to tantalum than to other metals which have been used in the past.

The operative procedure of prefrontal lobotomy has been employed in more and more cases in recent years. In this operation an attempt is made to free the cortex of the frontal lobe of the brain from some of its thalamic connections. The functional correlation is a loss of stereotyped emotionally-directed behavior and a turning of the patient's interest away from himself.

The war resulted in a very large number of cases of the interesting condition known as causalgia. This condition was first described at the time of the Civil War but comparatively few cases are seen in civilian practice. Causalgia follows injury to a peripheral nerve, particularly the median nerve, and is marked by burning pain, increased sweating and the signs of vasoconstriction. Studies have shown that this is due to increased sympathetic activity and that it can be relieved by blocking or cutting the sympathetic pathway to the involved area.

The subject of epilepsy is receiving increasing consideration. Much work has been done with the electroencephalograph in studying the brain activity which determines the convulsive and related phenomena. Several new drugs of an anticonvulsant nature have appeared, one of which, Tridione, seems to be particularly effective in treating the petit mal type of the disease. Petit mal Epilepsy is characterized by lapses of consciousness which last 5–30 seconds. During this interval the patient is immobile and out of contact with the world. The attack ends suddenly and he goes on about his business. There may be as many as one hundred of these attacks a day.

The disease, anterior poliomyelitis or infantile paralysis, has been the subject of intensive investigation from many angles. A recent viewpoint which has gained support in recent months is that infantile paralysis is really a systemic disease which is quite widespread and that it is only occasionally and in the late stages that neural manifestations appear. Thus it is believed that the paralyzed

cases constitute but a small percentage of the actual patients with this virus disease. In the treatment of polio, the use of the drug, prostigmin, has been advocated but its value is not as well authenticated as an article in a recent issue of the *Reader's Digest* would lead the public to believe. This only serves to emphasize that lay magazines are apt to be poor sources of technical information.

Alcoholism continues to grow as a neuropsychiatric problem but receives comparatively little medical attention. Recently a treatment for the breaking of the chronic alcoholic habit has been detailed and tested. It is a form of conditioned aversion response in which the reaction is built up in the patient by giving him drugs to cause nausea and vomiting along with his liquor for several days. It should be understood that this treatment is used merely to break a vicious cycle and that its use should be followed by intensive psychotherapy.

Favorable reports continue to appear on the subject of shock therapy for a large variety of psychiatric conditions. Insulin shock is still used in many locations but the trend is definitely toward electro-shock with many variations in technique being introduced. Recently it has been shown that most remissions in the disease occur shortly after discontinuation of the treatment. During a course of treatment by shock therapy it is important for the doctor to be able to distinguish accidental, organic reactions which may occasionally occur. Otherwise the reactions may be mistaken for a part of the original illness reaction and the treatment may be unnecessarily prolonged.

The use of certain drugs to facilitate the investigation of the unconscious field of the mind is becoming more widespread. The procedure is called either narcoanalysis or narcosynthesis. The drug permits the patient to talk about material that would be intolerable to him in the fully conscious state. For these procedures the patient is given a rapidly acting barbiturate drug by intravenous injection. The drug is given slowly until the patient is in a mild state of narcosis. Suggestion is then given much as in hypnosis, and then additional drug is given until the narcosis reaches a level in which the patient recalls his memories freely. As the patient comes out of the narcotic state he is given an opportunity to accept his unconscious material and suggestion treatment is used to help him formulate a more adequate synthesis of his reactions.

The recent war did not produce any new psychiatric entities but the conditions under which it was fought gave a new coloring to the basic picture of psychoneurosis. In former wars, particularly in World War I, the common picture was that of hysteria. The First World War was characterized by trench warfare and by dog-fighting aerial combat on a small scale. World War II was fought under much more terrifying conditions—massed aerial attacks against highly concentrated air defenses, precision bombing with tremendous explosives culminating in the atomic bomb, huge battleships, numerous submarines, rocket missles and flame-throwers. In this type of warfare the predominant psychiatric reaction was that of anxiety rather than that of hysteria. Speaking in general terms, anxiety is a deeper psychopathological reaction than is hysteria. There is ample evidence to indicate that modern warfare has become so threatening to life as to be incapacitating to thousands of young Americans. It is not out of place to state, that while it is possible that there may be no limit to engineering genius, there is reason to think of a limit to which the human mind may be traumatized by war. Modern warfare has become so terrorizing as to approach that limit, and men's minds may eventually break down under the abnormally threatening environments which they have created.

It has been said that, "Those who do not learn History's mistakes are condemned to repeat them." There is a distinct possibility that if the world does not heed the mistakes uncovered by World War II we may never be given another opportunity. It is a mistake to attempt the construction of a democratic society of adults when those adults were reared in homes where democracy was not

practiced. Children must learn to emancipate themselves from their parents before they can live without paternalism in government. And they must also learn to curb their selfish drives in order that they may live in a cooperative society. It is also a mistake for a people to fix their allegiance on purely material things, that is to be guided by a purely materialistic philosophy. Material things are individual and personal, while non-material, spiritual values attract group allegiances. A country that relies on purely material values is composed of a multitude of striving individuals and it will lack the common purpose which comes out of a spiritual faith. A nation of individuals may well fall before a nation which has a common goal based on a group idealism.

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RECENT ADVANCES IN ENDOCRINOLOGY

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THYROID

In reviewing the matter of endocrine advances during the past year or two, it seems evident that the discovery and subsequent clinical use of Thiourecil is the outstanding achievement. Since the original use of the drug by Astwood and his associates in 1943 (1) much interest has centered on the question of what ultimate value Thiouracil would have in the treatment of thyroroxicosis. Considerable skepticism was expressed in the early stages of its use, (2) and conflicting reports of its efficacy have been published during the last few months. Two and a half years have now elapsed since the first use of the drug, and in January of this year a comprehensive report was published by Robert H. Williams (3) giving the effect of prolonged treatment and the toxic reactions observed in 247 patients treated in the Harvard Medical School Clinics. Briefly, it appears to be established that Thiouracil in doses varying from .6 gm. to .3 gm. daily will produce remissions in patients with thyrotoxicosis; that thyroidectomy is accompanied by less thyrotoxic reactions when Thiouracil is used, even though the gland is rendered more vascular and friable than with the use of iodides; that combined administration of Thiouracil and iodides is desirable; and that toxic reactions may be expected in 14 per cent of cases. Toxic reactions are found to be more common with prolonged use of the drug and when unnecessarily large doses are used. Most important in the long list of toxic manifestations are leucopenia, agranulocytosis, fever, and various anaphylactic reactions. It has been suggested that the body capacity to bind protein is responsible for the anaphylactic reactions as well for the actual therapeutic effect of the drug (4). Work is rapidly going ahead in the perfection of new anti-thyroid drugs for which hope of non-toxicity is held—and only time will tell to what extent these drugs may supersede surgery in the treatment of thyrotoxicosis.

PANCREAS

Efforts have been centered on improvement of diabetic control by producing insulin preparations which will answer the 24-hour requirement. Protamine-zinc

insulin was thought to be the answer to this, but only in mild cases requiring less than 40 units daily has it been possible to rely on protamine to prevent hyperglycemia during the day, without producing hypoglycemia during the night.

A mixture of regular or crystalline insulin and protamine-zinc insulin in the ratio of 1 : 3 has been quite satisfactory, but is impractical from the standpoint of the ease of administration.

Globin-zinc and histone-zinc preparations have been tried with disappointing results.

In recent months, however, experiments have been made using a bi-phasic insulin containing twenty-five per cent of the protamine in quickly absorbable form, and seventy-five per cent in the present slowly absorbable precipitated form. It is uncertain as yet whether or not this form will prove to be stable for marketable use (7), (8).

MALE HYPOGONADISM

The male climacteric and sterility in the male have received a great deal of attention during these past months. Carl G. Heller has contributed immensely to the understanding of male hypogonadism by his comprehensive classification of the various forms of testicular failure (9). His is one of several excellent reviews of the problem published in the last two years. There is increasing interest in the use of testicular biopsies as an aid in therapeutic evaluation of problems of hypogonadism. Patients having complete hyalinization of seminiferous tubules with partial Leydig-cell failure may be expected to respond favorably to treatment with androgenic substitution therapy, whereas such patients would be totally unresponsive to chorionic or pituitary gonadotropins from the standpoint of subjective clinical relief of symptoms. It is to be understood that spermatogenesis cannot be attained when complete hyalinization has occurred.

In patients demonstrating only an early sclerotic change in the seminiferous tubules, with partial Leydig-cell failure, there is reason to hope that spermatogenesis may be stimulated by the use of chorionic gonadotropins. The duration and expense of both androgenic and gonadotropic therapy are of sufficient importance to justify the wider use of testicular biopsies as an aid in therapeutic prognosis.

Since mumps orchitis is of such significance as a cause of sterility and of early climacteric changes, interesting work is being done regarding its prevention. Gamma globulin from mumps convalescent serum is proving effective in some cases (10).

ADRENAL

Of practical importance from a diagnostic standpoint are the favorable reports concerning the reliability of the Kepler test in Addison's disease (11). Further studies have been made to determine the cause of faulty diuresis and the electrolyte changes which are the basis for the test (12), in the hope that the diagnostic measures may be further improved.

It is highly desirable to be able to discard a test such as the original Wilder test involving salt deprivation which was attended by dangerous reactions.

STEROIDS

The literature in recent months has been laden with reports of the painstaking efforts to isolate and differentiate the various androgenic steroids excreted in the urine (13), (14). It is thought that increasing simplification of methods of extraction and increasing knowledge of the source of the various fractions will prove to be extremely valuable in the diagnosis of adrenal and gonadal pathology. Abnormalities in which dependence for diagnosis is placed on the 17-ketosteroids, include adrenal deficiency in male and females, hirsutism, virilism, amenorrhea, and obesity in females, precocious puberty in males and females, adrenal cortical

tumor, gonadal tumors, and cancer in areas not associated with an endocrine gland.

Pregnandiol excretion in the urine during prolonged amenorrhea is being urged as a rapid, simple test for pregnancy (15). This method of testing was advocated as early as 1931, but has not come into wide use due to difficulties encountered in laboratory techniques. It is not yet certain whether or not the method is sufficiently accurate to justify its use.

PITUITARY

Continued efforts are being made to isolate and purify the various anterior pituitary hormones, but outstanding progress has not yet been achieved.

FEMALE HYPOGONADISM

Menstrual disorders, and sterility are still the outstanding problems in this field. In the last two years, there has been a better understanding of the importance of cyclic therapy in secondary amenorrhea and cases of sustained follicle hyperplasia. The uses of testosterone and progesterone are better understood—and there is a gradual and fortunate trend away from the indiscriminate use of estrogens.

Improved pituitary gonadotropins will eventually fill a great need for physiological ovarin stimulation.

Vaginal smears, stained by specific dyes, are now being widely used as a means of differentiating the various degrees of epithelial cell growth in response to estrogen hormone elaboration. This procedure has provided a practical and simple diagnosis test which may be used in an office.

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DERMATOLOGY AND SYPHILOLOGY

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With the advent of the war in the South Pacific, medication for the prevention and cure of malaria was given to large numbers of men. During the past two years, atabrine (Quinacrine Hydrochloride) has been the drug most commonly used.

Sulzberger reviewed the literature concerning a peculiar lichenoid eruption which occurred in individuals in the armed forces who were receiving atabrine. The eruption began from a few days to several months after the patients began taking the medication. It was common for the eruption to begin with eczematoid changes on the extremities, face and neck, and in some cases it began as a generalized exfoliative erythroderma. Usually after the type of onset, lichen planus-like lesions appeared. These varied from typical, angular, violaceous papules to large hypertrophic lichen planus-like plaques, which later often showed atrophy, pigmentation or depigmentation. Some cases had leukoplakia-like lesions on the buccal mucosa and others had scalp lesions which at times caused permanent alopecia. At the Naval Medical Center in Bethesda, Maryland, atabrine was administered to a group of these patients with quiescent lesions, causing a high percentage of focal flareups of the eruption, and in some cases widespread eczematoid and exfoliating reactions. It is felt that there is little doubt that this peculiar lichenoid dermatitis is a drug eruption due to atabrine.

There are increasing reports of dermatitis due to the use of penicillin. Binkley and Brockmale reported a case of epidermal and dermal sensitivity to sodium penicillin, as proven by patch, scratch and intradermal tests. They reported another case who developed a dermatitis about six weeks after first exposure to penicillin but in whom the patch and scratch tests were negative. However, in this patient when penicillin was injected intramuscularly, there was edema and a confluent papular eruption involving the hands and feet. The skin of the feet had never been previously exposed to penicillin but had been the site of a chronic dermatophytosis. Other cases of a dermatitis developing at the site of previous fungous infections have been reported, and Sulzberger suspects that this localization may be due to a common allergenic fraction in the fungi found on the skin and in penicillium notatum. Cormia reported a serum sickness-like syndrome with generalized urticaria, mild arthralgia, and lymphadenopathy. This is now known to be a common reaction to penicillin. Miliaria-like and erythrema nodosum-like eruptions have also been reported.

About five years ago, there began on the East Coast of the United States an epidemic of ring worm of the scalp involving boys and girls of prepuberty. This has gradually spread to the Midwest and within the past eighteen months has assumed epidemic proportions in the State of Ohio. There are two organisms which commonly cause ring worm of the scalp: *Microsporon audounini* and *Microsporon lanosum*. These two organisms differ in that infections due to *Microsporon lanosum* commonly cause a severe inflammatory reaction and can be cured with ease by local medication; whereas those due to *Microsporon audounini* show almost no inflammatory response and are most resistant to any local therapy. In this epidemic, the first of its kind in the United States, the offending agent has been *Microsporon audonini*. The Wood's light, which is ultraviolet light filtered through cobalt glass, causes infected hairs to shine with a bright green flourescence, and is an indispensable diagnostic tool. At the present time, the treatment which is accepted and efficacious in these cases, is temporary epilation by means of x-ray.

Urbach recently described a syndrome usually presenting a clinical picture of furnuculosis, sweat gland abscesses, eczema and pruritis, in which there was a

normal blood sugar curve but microchemical examination of the skin itself showed the sugar content to be higher than normal. A low carbohydrate diet sometimes combined with insulin, caused marked improvement in the dermatoses.

Kaposi in 1897 described a varicella-like eruption which occurred in infants as a complication of eczema. Some authors have stated that this entity is the same as eczema vaccinatum. In December, 1944, Lane and Herold described five patients with this type of eruption, only one of whom could possibly have been infected with the vaccinia virus. In February, 1945, Lynch described a group of four cases with a herpetic eruption complicating atopic eczema. In three cases, he showed presumptive evidence that the herpes simplex virus was the causative agent and in one case, laboratory studies permitted the conclusion that the virus of herpes simplex caused the eruption. He suggested the name "eczema herpeticum." Blattner, et al., reported a case of a boy, age fifteen months, who had had atopic eczema since the age of six weeks, had never been vaccinated against smallpox, and who developed fever and an acute exanthema of the herpetic type. By animal experimentation, histo-pathologic and immunologic studies, they established the causative agent to be the herpes simplex virus. There seems to be little doubt that the herpes virus has been proven to be the causative agent of a varicella-like eruption, complicating atopic dermatitis.

Stryker and Halbeisen described a group of cases with cutaneous lesions consisting of a patchy or diffuse, scaly erythroderm involving the sides of the neck and anterior shoulders. These patients also exhibited a few signs of a mild vitamin deficiency, although all declared their diets to be adequate. Blood studies revealed a macrocytic anemia. Crude liver injections caused a disappearance of the eruption and a return to normal of the blood picture. These studies may throw light on some of the bizarre eruptions appearing around the shoulder girdle which commonly have been called neuro dermatitis.

In dermatologic therapy, a few new, useful agents have been introduced. Penicillin has been most promising in the treatment of the pyodermas. As in other fields of medicine, it has been tried indiscriminately in the treatment of dermatologic entities in which therapy has been unsatisfactory. It is not efficacious in pemphigus vulgaris, dermatitis herpetiformis, eczema, seborrheic dermatitis, acne vulgaris and the chronic dermatoses involving the hands.

Two new fatty acids, namely, propionic acid and undecylenic acid, have been introduced and widely used as a treatment for superficial fungus infections.

Eddy and his workers at the U. S. Bureau of Entomology, have developed formulas containing benzyl benzoate, pyrethrins, undecylenic acid, 2–4 dinitro anisole and DDT, in the treatment and control of head lice, crab lice and scabies. They have been largely responsible for the excellent control of these conditions in the armed forces.

The combination of Vitamin B complex and hydrochloric acid has been reported by at least three workers, to be helpful in the treatment of vitiligo.

Two new preparations, pyribenzamine (Ciba) and benadryl (Parke, Davis), appear to be useful drugs in the control of reactions caused by histamine. They are especially promising in the treatment of urticaria and although they are nonspecific as far as the allergens producing the urticaria are concerned, they appear to be specific as far as the mechanism by which some of these allergens produce the disease.

Peters, after studying the chemical content of the exfoliated skin from patients with exfoliative dermatitis, treated them with cystine with good results. He suggested that in an attempt to restore the epithelium, the body had depleted its sulfur containing amino acids.

Cannon reported successful results in five cases of acute disseminated lupus erythematosus by the oral administration of iodine. He tried the treatment when he noted improvement in a case of acute disseminated lupus erythematosus

who had been given a dye containing iodine preceding roentgenograms of the gall bladder.

The most important advance in the field of syphilology is treatment with penicillin which appears to be most valuable in the treatment of early syphilis. The trend in treatment is to use a combination of penicillin and the heavy metals. Eagle, et al., have shown penicillin and Mapharsen to be synergistic in the treatment of experimental syphilis. Platou, et al., treated sixty-nine infants with early congenital syphilis and reported the immediate response to be encouraging. Rose, et al., gave a preliminary report on seventy cases of central nervous system syphilis treated with penicillin. The greatest improvement was in patients with general paresis. Dolkart and Schwemlein found it necessary to discontinue penicillin in the treatment of two cases of cardio-vascular syphilis because of the development of severe anginal pain. In general, it may be said that penicillin is a useful agent in the treatment of syphilis, but that no long term evaluation can be made as yet.

The incubation period of syphilis is considerably longer than that of gonorrhea and the effective dose of penicillin for syphilis is much larger than for gonorrhea. The small doses of penicillin which are successful in the treatment of gonorrhea may in a concomitant case of syphilis temporarily suppress the primary, secondary and serologic manifestations of early syphilis. This makes it mandatory that all cases of gonorrhea treated with penicillin be followed serologically for six months to one year, rather than three months as has been previously recommended.

Some important work has been done on the serologic verification tests. Rein and Elsberg examined six verification tests to determine their value. They found none of these methods to be of value in distinguishing consistently between true positive (syphilitic) and false positive or non-syphilitic reactions. It was their feeling that present verification tests are of no value in the sero diagnosis of syphilis. Scott, et al., in another study came to the same conclusion.

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RECENT ADVANCES IN ANATOMY

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In this brief survey only those topics which appear to be of special interest to members of this section have been selected for discussion.

The number of human embryos of the first two weeks of development recovered by American embryologists has been almost doubled during the last six years. This is a remarkable achievement when it is realized that it was accomplished largely by the joint efforts of two men—Hertig and Rock, of the Staff of the Free Hospital for Women at Brookline, Massachusetts. Prior to their discoveries our knowledge of early human development was based on hardly more than a dozen embryos scattered widely among the laboratories of Europe and America.

Obviously the phenomenal success of these searchers for human specimens seldom or never seen, was not a matter of mere chance. They undertook a systematic and organized search for human ova in uteri of patients of high fertility who were willing to cooperate by keeping, while awaiting hysterectomy, a careful record of menstruation and coitus dates. These records enabled them to determine the likelihood of the presence of a conceptus and to judge more accurately the age if one were found.

In 1942, they announced the recovery of two normal human ova of 7½ and 9½ days of age respectively, which represented at the time the youngest human embryos ever observed. The younger embryo was in the process of implantation, the older one had just completed this process. Last month at the annual meeting of the Association of Anatomists at Cleveland, they reported the finding of a young human blastula free in the cavity of a uterus in the twenty-first day of the cycle. The probable fertile coitus occurred 4½ days previously. This conceptus is judged to be 4 days old. It consists of nine blastomeres of varying size and shape. Since some of the blastomeres are multinucleated, it is concluded that the specimen is abnormal, hence the 7½ day old embryo still remains as the youngest known normal human embryo.

A study of twelve very young embryos of their collection has been reported in some detail. Of this number seven were normal and five abnormal, the latter being so pathological as to indicate early abortion. It is interesting to note that all the normal embryos were implanted on the posterior wall, and all the abnormal on the anterior wall.

They conclude, 1) that nidation takes place between the fifth and eighth day following fertilization, 2) that the post-ovulatory phase of the menstrual cycle is less variable in duration than the pre-ovulatory phase, 3) that ovulation regularly occurs 14 days prior to the onset of menstruation, thus a women with a menstrual history varying from 25 to 30 days has an ovulatory period ranging from the 11th to 16th day of the cycle.

The recent literature clearly shows a trend in anatomical investigations away from strictly morphological studies toward histo-physiological and histo-chemical problems. The aims of histophysiology are to interpret structure in terms of function and to provide a structural basis for understanding functional processes. In histochemistry the objective is the localization and identification of chemical substances in respect to the structural organization of the tissue elements.

Obviously histophysiological studies require the use of both histological and physiological methods. The usual procedure is to study the morphological changes associated with varying states of functional activity. Modern endocrinology owes much to this type of investigation. Of the very recent histophysiological contributions one only has been selected for discussion.

Dougherty and White, 1946, demonstrated that the adrenal cortex exerts a controlling influence over the number of lymphocytes in lymphatic tissue and in the circulating blood. Adrenalectomy in animals produces lymphoid hyperplasia and lymphocytosis whereas the injections of adrenotropic hormone or adrenal extracts produce lymphopenia in lymphatic tissue, lymphocyte degeneration and an increase in plasma cells. It has been shown also that augmentation of the normal quantity of circulating adrenal cortical secretion produces a significant increase in serum globulin and in circulating antibodies, which suggests that disintegrating lymphocytes are sources of these substances.

Histologists have long been interested in the localization and identification of chemical substances in cells and tissues. They have been over-zealous many times in interpreting their staining reactions on a chemical basis. Of the many methods that have been proposed in the past but a very few, such as the Sudan staining for lipids, the Prussian blue reaction for iron, and the nucleal reaction for chromatin have been accepted with certain limitations as trustworthy.

In the last two decades, particularly the last, investigators with experience in both histology and chemistry have reported many new histochemical methods. The procedures are diverse but all depend on the physical and chemical properties of the tissue constituents.

Differences in solubility and in rate of sedimentation on centrifugation have been employed to separate and isolate various cellular components for chemical analysis. The amazing feat of separating intact mitochondria from liver cells was accomplished by Bensley and Hoerr in 1934, submicroscopic particulates by Claude in 1938, glycogen particles by Lazarow in 1942, intact nuclei by Dounce in 1943 and nuclear chromatin in pure state by Claude and Potter and by Mirskey and Pollister in 1943. Methods and results are discussed in Volume X of Biological Symposia.

Analytical chemical analyses of the isolated mitochondria and submicroscopic particulates show that both are complexes of proteins, nucleo-proteins and lipids, the mitochondria containing more protein and less lipid than the particulates of Claude.

Identification of substances in situ in microscopic sections, either fresh or fixed, has been accomplished by various means; behavior in polarized light, fluorescence,

microincineration, ultra violet absorption and by highly specific and sensitive chemical reactions, the last mentioned has the advantage of superimposing a chemical picture on a morphological picture. An evaluation of these methods was published by Lison in 1936.

More recently introduced techniques that are now being extensively studied and applied are discussed in a recent review of histochemistry by Dempsey and Wislocki, 1946. It has been found that treatment of sections with the enzyme ribonuclease destroys the characteristic basophilic staining reactions of the Nissl granules in nerve cells, of the cytoplasmic granules of the basophiles of the anterior pituitary, of the cytoplasm of serous secreting glands, and of the trophoblast of the placenta. Thus, it appears that all those substances in cells which lose their characteristic basophilic staining reaction after digestion with ribonuclease represent or at least contain the ribose type of nucleo-protein.

It has also been demonstrated that the adrenal cortex, ovarian follicle, corpus luteum and trophoblast cells of the fetal placenta contain a lipid soluble substance that will convert phenylhydrazene when applied to sections to yellow phenylhydrazones. This is a well known test to aldehydes and ketones, but since this substance is lipid soluble and since it is present in the organs which are known to produce the keto-steroid hormones, it is concluded that this test demonstrates the presence of such substances in tissue sections.

The localization of the alkaline and acid phosphatases can now be visualized in microscopic sections. Since the phosphatases are believed to participate in the metabolism of phospho-lipids and sugars and in the absorption of sugars and fats through cellular membranes, the visualization of the precise location of these enzymes affords a valuable histological method for the study of cellular functions. A number of papers dealing with this subject has just been published. It seems that the enzymes are accumulated between the blood stream and the site of deposition of glycogen. They are present in the distal part of the absorbing cells of the small intestine. The prostate gland contains only acid phosphatases. Acid phosphatases accumulate in the syncytium of placentas near term, whereas alkaline phosphatases are present throughout gestation.

The interest of histologists in histophysiological and histochemical studies has prompted Dempsey and Wislocki to propose the term physiological histochemistry for this new discipline which correlates morphology, chemistry and physiology.

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SOME ADVANCES IN THE CONTROL OF TOOTH DECAY

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Among civilized peoples today decay of the teeth is one of the most prevalent of disease conditions, affecting 85–90 per cent of all such individuals. It is distinctly a disease of civilization as attested by the fact that primitive populations show an incidence as low as 3–10 per cent. Its progressive increase has paralleled that of the increased use of refined food, especially the carbohydrates. Despite the fact that reference to tooth decay has occurred among the writings of all people and in all times, some of the earliest scientific experiments and observations were made by Dr. W. D. Miller (1) about 1880. He isolated 22 bacterial forms from the mouth and decayed teeth and demonstrated that 16 had the ability to form acids when mixed with carbohydrates. He subjected extracted teeth to such mixtures and produced lesions comparable to those occurring in the mouth under natural conditions. The fundamental observations of Miller which related the oral acid forming bacteria and carbohydrate food material to tooth decay have never been successfully contradicted and are today a working basis for any method of control. After Miller's death (1907) little of real value was added to the knowledge of tooth decay until 1923. Starting then and working continuously for several years a group consisting of dentists, bacteriologists, nutritionists and physiological chemists began an intensive study of the saliva and blood of decay susceptible and decay resistant children, using orphanage populations. As a result they were unable to demonstrate any consistent significant group differences in the chemical nature of the blood or saliva (2, 3). However, in a bacteriologic survey (4, 5, 6, 7, 8) of decay free and decay susceptible individuals they found *L. acidophilus* consistently present in large numbers where tooth decay was active. This bacterium was absent, or only sporadically present in small numbers, where tooth decay was inactive. This relation has been substantiated by others (9, 10) and the relatively few contrary findings (11) are minimized by the fact that similar bacteriologic methods were not employed.

It has been adequately demonstrated that there is a direct relationship between the occurrence of *L. acidophilus* in the saliva and the activity of tooth decay, and that the quantitative estimation of salivary *L. acidophilus* is a relatively accurate index of the degree of such activity. That there are other acid forming bacteria involved is understood. The *L. acidophilus* count is used only as an index of the total acidogenic process.

There is definite evidence (12, 13, 14) of the effect of the ingestion of sugar on the activity of oral acidogens. Their activity and the resultant tooth decay are directly related to the amount of refined sugars in the diet of susceptible individuals. About 85 per cent of us are susceptible, about 5 per cent never have tooth decay, regardless of sugar intake, while about 10 per cent are so susceptible that refined starch continues to be a factor in their tooth decay when all refined sugars are withdrawn from the diet.

This is the now generally accepted status of the factors involved in tooth decay. The picture is incomplete, mostly in the area of true immunity which seems to have no relation to dietary factors. In these cases there is no acidogenic oral flora and attempts to grow *L. acidophilus* in either the saliva or the blood of such individuals have failed (15). There is some evidence (21) that this may be due to an ability to convert certain amino acids into ammonia nitrogen which acts as a deterrent to the growth of acid forming bacteria in the mouth.

Since 1939, the beneficial results of small amounts of fluorides naturally present in water supplies has been proved. Teeth of children which have developed

during the period of consumption of such water have shown a markedly lowered caries rate (16). Such teeth contain a greater amount of fluorides (17) and calcium salts are known to become less acid soluble through the addition of fluorine.

Within the past few years it has been reliably reported that the use of carcanimide (18) in dentifrices and mouth washes, synthetic vitamin K (19) in chewing gum, ammonia mouth washes, reported topical applications of sodium fluoride solutions on the cleaned surfaces of the *teeth of children* (24, 25, 27, 28) and the temporary elimination of refined carbohydrates from the diet (29) have each reduced the rate of tooth decay.

All these methods are based on possibilities of control which are compatible with what is now known about tooth decay, to wit, that it is initially a localized decalcification of hard tooth tissue by acid formed by oral bacteria acting on carbohydrate food material. These possibilities are:

1. Decreasing the intake of foods from which oral bacteria can form acids. This is the dietetic control and is being used for individual cases.
2. Direct inhibition of the growth of oral acid producing bacteria. This can be accomplished by the use of synthetic detergents (wetting agents), urea and ammonia.
3. Interference with the chain of reactions necessary to produce acids, such as occurs in the presence of synthetic vitamin K (quinone).
4. Reducing the solubility of the calcified tooth tissues in acids such as occurs in teeth developed on natural fluoride waters and such as may be the result of fluoride solutions topically applied to the enamel of children's teeth.

Of the above, the direct inhibition of bacterial growth and the interference with acid formation can be accomplished only for a very short time and to produce results they must be carried out immediately after any carbohydrate, especially refined sugar, has been eaten. Attempts to control tooth decay by such means are still very much in the experimental stage and more data will be necessary before their usefulness can be accurately evaluated.

Diet control will produce results and is being used rather widely. Its chief limitations are that it is an individual treatment and that patient cooperation is absolutely necessary. A period of six weeks divided into three two-week periods is used. The first period eliminates all free sugar and reduces other carbohydrates to 80–100 grams per day. If strictly followed it will reduce a high *L. acidophilus* count to zero in most cases. The second period introduces an increased amount of carbohydrate (not refined sugar) and the third period allows as much sugar or sugar sweetened food as desired at one meal per day. Salivary *L. acidophilus* counts at the end of each period show little or no increase, provided the prescribed diet has been followed. Following the dietary treatment, patients are checked at six-month intervals for two years. It is not unusual to find the *L. acidophilus* count still quite low at the end of this period. The length of the beneficial effect is proportional to the patient's ability to limit his sugar intake to reasonable amounts, following the restricted diet period.

Repeated topical applications of sodium fluoride solution to the cleaned surface of children's teeth is a practical procedure and will reduce the future occurrence of tooth decay by about one-third. This also has the limitation of being an individual method of treatment and is thus restricted in its application. It is practical and requires only that the patient report for treatment.

The fluorination of communal water supplies now deficient in natural fluorides (less than 1.0 P.P.M.) offers the best possibilities of wholesale reduction of tooth decay. In order to determine whether or not artificially fluorinated water can accomplish the same results as have been proven for naturally fluorinated waters, large scale controlled experiments are now under way (22, 23). The results will not be known for 8–10 years since they can only be judged on the basis of the decay which will occur in the teeth now being developed by children on such a water

supply. If successful, this will offer a public health measure of tooth decay control which can be applied to all children raised on communal water supplies. This would reach about two-thirds of our child population. If it is as effective as natural fluorides it will effect a reduction of tooth decay in children to about one-half of its present rate.

In summary, we are now in possession of considerable information, the application of which could markedly reduce tooth decay if it could be easily and generally employed. There is no proof that tooth decay is related to dietary deficiencies but there is a great deal of proof that it is related to the excessive consumption of refined carbohydrates, especially sugar.

Sugar rationing and threats of sugar shortages are amusing. From the standpoint of tooth decay the complete elimination of all refined sugar from the diet would be a godsend to the present generation of children. Neither would it do harm to the waistline and few remaining teeth of their elders who still persist in the erroneous belief that candy is essential to child development and happiness.

While the proper use of fluorides will reduce tooth decay their role is palliative. Specifically fluorine acts to slow down the destructive effect of localized acid production. This acid would never have been generated in the absence of acid forming oral bacteria nourished by refined carbohydrates from food.

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SOME APPLICATIONS OF ATOMIC ENERGY TO DIAGNOSIS AND THERAPY

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Applications of atomic energy, used here synonymously with nuclear energy, for therapy began when radium was first used for treatment, since the rays emitted by radium and its disintegration products are manifestations of nuclear atomic energy. In 1932 Professor Ernest Lawrence invented the cyclotron and since then radioactive species of almost all of the elements have been generated in it. Many of the artificial radioactive species of those elements which make up our bodies disintegrate too rapidly to be useful to us in medicine. But some of them produced by bombardment in a cyclotron, and recently by fission of certain heavy atomic nuclei, last sufficiently long that they can be utilized by physicians. A few of the applications to diagnosis and therapy thus far explored are briefly summarized in the following discussion.

The extreme sensitiveness of appropriate detecting devices for the emitted rays makes it possible to measure accurately the concentrations of the elements in dilutions often as great as a billion or more times beyond former methods, and studies are thus possible with elements normally present in the body in minute amounts without disturbing existing physiological equilibria.

Radio-Iron.—During the war radioactive red blood cells were obtained (1) in which the hemoglobin molecules had become "tagged" with radioactive iron injected into volunteer donors. Determinations by physical methods of the time that the radioactive cells remained in the circulating blood of volunteer recipients after treating the donor blood with various adjuncts made it easy to determine the best preservative for addition to the whole blood collected on the coasts of the United States and flown to the battle fronts.

Last year a British worker (2) used such "tagged" erythrocytes to circumvent the difficulties formerly encountered in determining blood volume, and found the value to be 73.5 cc. per kilogram of body weight in normal subjects. Compensated heart cases had blood volumes in close agreement with normal, but in a case of heart failure, there was a considerable increase in both the amount of blood corpuscles and the circulating blood volume. In another case of heart failure treatment resulting in compensation was associated with a 28 per cent decrease in blood volume and an 18 per cent decrease in red blood cells.

Other investigators (3) have shown that anemic dogs absorb "tagged" iron rapidly from the gastro-intestinal tract whereas absorption is slow when the iron level is adequate. Only 0.3 per cent was absorbed in 23 hours after the last feeding in non-anemic dogs, but 59 per cent of the radioactive iron was absorbed by anemic dogs in the same time. Four per cent of the absorbed labelled iron was contained in the erythrocytes in the first case as compared with 78 per cent in the anemic dogs.

Radio-Iodine.—The thyroid gland normally contains about one part of iodine in a thousand whereas the blood averages less than one part in ten million. Because of this marked localization and because radio-iodine emits gamma-rays, it is easy to carry on many diagnostic and metabolic studies *in situ* merely by placing a sensitive detecting device over the gland. Hamilton and co-workers (4) found that, when 0.1 microgram of sodium iodide, the iodine of which was labelled with radio-iodine, was administered to patients with thyroid disease, the following percentages of the dose had localized in the thyroid at the end of one day:

Diseases	*Per Cent Uptake*
Hypothyroidism without goiter	2.0
Normal controls	18.5
Non-toxic goiter	25.0
Toxic goiter	61.5

Certain cancers of the thyroid show accumulation of radioactive iodine not only in these structures but also in metastases to the bones (5). In such cases it is a hope, when sufficient radio-iodine becomes available as a by-product of fission of uranium-235 or of plutonium, that cures may result from the radiation emitted by large doses. Similarly, large doses of radioactive iodine have been reported to be effective in treating toxic goiters by such internal radiation. The dangers of radiation of surrounding vital structures incidental with roentgen-therapy are largely avoided by this method.

Radio-Sodium.—Radioactive sodium produced in a cyclotron has recently been used as an aid in the diagnosis of peripheral vascular diseases (6). It was injected in such a small amount as to be of no harm, as isotonic sodium chloride, into an antecubital vein and a foot was then placed close to a tube sensitive to the gamma-rays emitted. Dependent upon the arm-to-foot circulation time, the tube was activated in twenty to fifty-five seconds in normal subjects as the radioactive sodium was carried into the foot. The radioactivity of the foot continued to increase until the concentration became more or less uniform throughout most of the body. A plot of increased radioactivity of the foot against time after injection reached a plateau in about forty minutes normally as equilibrium was reached. When the circulation to the foot was impaired, the plateau was not so high nor reached so quickly as normally.

In a patient with peripheral vascular spasm the plateau was only about one-third as high as normally. After bilateral thoracolumbar sympathectomy was performed, the plateau was far above normal. Other conditions in which the plots were of diagnostic value were arteriosclerosis; thrombo-angiitis obliterans; various vascular obstructive lesions; scleroderma; and Raynaud's disease. In some cases the new technique may furnish information concerning vascular supply which is valuable in determining the level at which amputation is necessary.

Radio-Phosphorus.—Because phosphorus is present in all cells and it can readily be made radioactive in a cyclotron, it has been employed far more commonly than any other artificial radio-element in biological tracer studies as well as in therapy. Usually it is converted to disodium hydrogen phosphate for administration.

Numerous investigators have sought to treat tumors with radio-phosphorus by differential localization in them, since cells in rapid mitosis utilize much phosphorus for the formation of nucleoproteins and it might therefore be expected that these cells would localize more or less selectivity much of an intravenous dose of radioactive sodium phosphate and thereby be destroyed. The fundamental principle involved here is that the destructive ionizing radiation emitted by the radioactive phosphorus will penetrate only for limited distances so that it will affect adversely only the tissues in which it is localized. Radio-phosphorus has been explored extensively in leukemias, lymphosarcoma, multiple myeloma, etc., but early hopes for effectiveness in soft tissue tumors have not been wholly realized. This is so largely because the phosphate salts in bone are relatively so insoluble that too much destruction of bone marrow results from the high localization in bone when sufficient amounts to affect such tumors adversely are administered. The extensive studies of Dean Doan and Professor Wiseman of the College of Medicine with radioactive phosphorus generated in the cyclotron of the Physics Department of The Ohio State University during the last six years have shown, as well as the work of others, that radio-phosphorus is highly efficacious in the treatment of polycythemia rubra vera and promises to supplant all former therapeutic measures in this disease. They have used it successfully in the treatment of chronic leukemias, especially myelogenous leukemia.

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RECENT ADVANCES IN BACTERIOLOGY

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As is true of many sciences in this period of scientific advancement, Bacteriology has extended its frontiers in many directions. In so doing Bacteriology has joined hands with numerous scientific neighbors with the result that subject boundaries have become indistinct, and many areas are held jointly by two or more sciences. Furthermore, the advanced nature of modern research requires a mutual exchange of techniques among sciences and demands their close association in research for the solution of the problems that now present themselves for study. The circumstances of the highly technical war that we have just waged have shown us how necessary and effective is this teamwork among sciences.

Things being as they are, then, advances in Bacteriology are not circumscribed by limitations implied by the term "Bacteriology," but are associated with progress in allied fields. During the war, many advances were particularly concerned with the applications of scientific knowledge on a large scale.

With this understanding, let us briefly consider the advances recently made in four fields arbitrarily designated as (1) General Bacteriology, (2) Medical Bacteriology and its Applications, (3) Viruses, and (4) Medical Mycology.

(1) *General Bacteriology.*—For some years the sulfa drugs have been studied and employed as chemotherapeutic agents, with results known to all. Bacteriology has developed the techniques of experimental evaluation and of the control and interpretation of clinical trial. The mode of action of sulfa drugs was early recognized as a problem of bacterial metabolism, and while the explanation is still theoretical and not always applicable, it is now most generally thought to be of this sort: bacteria that are sensitive to sulfa drugs owe this sensitivity to the facts, first, that they, like most other living things, require vitamines or vitamine-like substances for their growth and development; second, that they are unable to distinguish between these essential substances and structurally similar compounds such as the sulfa drugs; and third, once having taken up the metabolically inert sulfa molecule the bacterial cell is incapable of utilizing the growth factors. Bacteria thus held in a condition of stasis readily succumb to the defense mechanisms of the host.

Antibiotics, those substances produced by molds and bacteria and antagonistic to other microorganisms, are likewise well known as therapeutic agents. Bacteriology has established methods of laboratory assay and by such means can tell the concentration of an antibiotic in the body fluids of patients. The mode of

action of this biological product is as yet undefined, but it does appear that the antibiotics now in use exert their effects by bacteriostasis when the concentration of the drug is low and by bacteriocidal and bacteriolytic actions when the drug is is high concentration.

For some time it has been known that the types of pneumococcus are differentiated according to the specific carbohydrate composition of the capsule, and that a pneumococcus could be changed from one type to another by certain laboratory procedures. The interesting observation has recently been made that exposure to desoxyribonucleic acid from an encapsulated Type III transforms an avirulent non-encapsulated Type II into a fully virulent Type III pneumococcus. In this way, one variety of bacterium is converted to another by the presence of a substance of known chemical composition, not unlike the determining action of a gene in higher forms.

These instanҫes of alteration of bacterial metabolism by the presence of certain substances point to the so-called "phenomenon of interference" in bacterial physiology. With this phenomenon brought to the attention of investigators, other examples are constantly being described having to do with the competition of bacteria and viruses for food elements, some of which are chemically defined. This type of work involves a detailed chemical and biological approach to the study of enzymes, bacterial metabolism and parasitism and will yield fruitful results with further exploration and analysis.

Advances in biophysics, as applied to Bacteriology, are only begun, but already there is much promise in the use of tagged and radioactive elements in the study of bacterial metabolism. It is expected that the utilization of tagged elements will disclose how molecular chemical reactions are brought about by bacteria and how the chemical structure of bacteria is built.

The electron microscope has been used to explore, by its high magnification, the finer details of bacterial composition and the shape and size of viruses. Attention has been concentrated on the finding of minute structures in bacteria and the possibility of their representing nuclear elements. Thus far, no definite nucleus or chromosomal mechanism has been established, but the interpretation of the physical findings combined with histo-chemical studies may shed light on this basic and baffling question in bacterial morphology and genetics.

(2) *Medical Bacteriology and Applications.*—It is unnecessary to dwell on the valuable improvement of diagnostic methods by the laboratory workers of the Armed Forces. Not only has the best effort of highly qualified experts been spent on this practical question, but also the circumstances of military activities in so widely scattered parts of the world have necessitated a development of techniques in microbiological fields hitherto not possible.

The control of air-borne infections has been studied intensively by military and civilian groups. The scientific approach has consisted of the development and application of methods for the determination and control of the factors involved in transmission of respiratory bacteria, such as particle size, conditions favoring suspension and transmission of dust and respiratory droplets laden with bacteria, devices to sample air and to count its contained bacteria, methods of dispensing disinfecting aerosols in barracks, schools and other common rooms, the efficiency of germicidal light, and the oiling of floors and bedding to keep down contaminated dust. Above all, much effort has been spent on the interpretation of the results of using one or another of the many devices devised. This whole program has had and will continue to have far reaching results in the difficult field of respiratory infections.

Medical Bacteriology has been much concerned with drug fastness to sulfa drugs and antibiotics. Too often for completely satisfactory results, bacteria either in a single patient or passed from person to person have proved by bacteriological methods to be resistant to the drugs in use. This seems to be more a

matter of selection and survival of drug-fast bacteria in a bacterial population than the sudden conversion of a whole population to the state of resistance. Once the fastness fortuitously occurs, it persists in the strain transmitted to subsequent hosts. Medical bacteriological laboratories now use techniques for the determination of such fastness and report the findings to the clinician or public health official who takes the observation into account in further management of the situation.

The applications of Medical Bacteriology would not be completely recounted without a reference to the improvement and probably increased effectiveness of certain bacterial vaccines, such as those against typhoid and paratyphoid fevers, cholera, plague and tetanus. Also, reference should be made to the measures taken to combat hazards of water-borne infections and bacterial food poisoning experienced by our men under conditions of combat and service in the near and remote parts of the world from the Equator to the Arctic Circle. Here, methods of sanitary control, preparation of safe food, vaccines and education reduced greatly the likelihood of food and water-borne disease. Similarly, the development and application of insecticides were instrumental in reducing the incidence of insect-borne disease.

(3) *Viruses.*—The study of viruses and virus diseases, well advanced before the war, was given a marked impetus by the necessities of military activity. The solution of earlier problems was advanced, such as in influenza in which laboratory diagnostic methods were improved, epidemiology studied, and vaccines developed and applied. Similarly, typhus received much attention with the result that serological tests were devised, the relation of epidemic typhus of man and endemic typhus of rats was more clearly defined, and the typhus vaccine was improved. Attention to scrub typhus, met by our men in the Far East and Western Pacific, necessitated intensive studies that disclosed the native rodents as sources of infection, insects as vectors, and the elimination of these factors in camp sites as measures of control. Progress has also been made in the development of vaccine.

Atypical pneumonia and infectious hepatitis occurred seriously during the war, the former in increased incidence and the latter in epidemic form. The specific cause of atypical pneumonia is as yet undetermined, although bacteria are thus far excluded. It is interesting that so many cases should be recognized clinically in recent years, as if it were a new disease, and yet no one virus of several proposed has convincingly been shown to be the sole specific cause. Infectious hepatitis, first seen arising from a contamination in the human serum component of yellow fever vaccine, proved serious also in large spontaneous epidemics. Lacking a susceptible experimental animal, human volunteers have been used in studies on etiology, and it now looks as though the disease is due to a virus present in patients' feces and entering by the mouth. The etiologic agent may be related to those of catarrhal jaundice and of hepatitis occasionally following injections of human serum.

Recent advances in the study of poliomyelitis have not settled the question of the modes of transmission and entry of virus into the human body. Detailed epidemiological studies, histological examinations of nervous tissues, and the finding of virus in the upper respiratory tract coincident with the infectious period of persons for others point to a substantiation of the theory of contact and droplet methods of transmission, as opposed to the theory of intestinal source and entry of virus.

The classification of viruses has been a troublesome question for those who desire to arrange their subject matter in orderly fashion. It seems now as though, by our continued detailed study of the various features of viruses and virus diseases, that at least four groups can be identified: viruses of some forms of encephalitis (St. Louis, Japanese B, Russian Spring-Summer, and louping ill); viruses of relatively large size and of similar antigenicity (psittacosis, lymphogranuloma venereum, mouse pneumonitis, and meningo-pneumonitis); viruses of pox diseases (smallpox,

vaccinia, swine pox, etc.); the bacteriophage group; and viruses parasitizing plants. Each group is defined by reference to various criteria, such as host, antigenicity, modes of transmission, pathology, and susceptibility to sulfa drugs.

Although some viruses may be grouped according to similar characters, virologists are still more impressed by the constantly increasing heterogeniety observed in the properties of viruses, so that they may be thought of as being as varied and dissimilar as the wide range of bacteria.

(4) *Medical Mycology.*—Mycology has developed in relation to Bacteriology in two directions, namely, in the findings of antibiotics active against microorganisms and in the study of infections due to pathogenic fungi. Having already referred to the problems of range of bacterial antagonism, mode of action, drug fastness and biological assay, let us here mention the advances made in connection with antibiotic production itself: the discovery of new fungi elaborating the antibiotic principle, the choice of strains by careful test, the physiology of fungi, the factors affecting biological variation as exemplified by antibiotic production, purification and separation of the active principle, tests for and control of toxicity for host cells, development of media and procedures for commercial production, and the chemistry of the antibiotic preparations. Each point mentioned represents new, basic and practical advances pressed for war and scientific purposes, with results known and anticipated for the relief of suffering and the prolongation of life.

There occurs a disease in the dry regions of the Southwest due to a fungus, *Coccidioides immitis.* It seems to have its habitat in the soil or vegetation and when inhaled by man causes a condition which has not attracted much attention until our troops stationed in those parts for desert training became manifestly infected. This finding and the study of the fungus and disease have led to the recognition of the importance of the condition. Likewise, it has stimulated interest in other infections due to pathogenic fungi hitherto considered rare and unimportant. Such infections lead to a hypersensitivity to the proteins of the fungus and recently a large part of the young adult population in the Midwest has been found to be hypersensitive by skin test to the proteins of another pathogenic fungus, *Histoplasma capsulatum.* The significance of this finding is yet to be determined, but it does appear as though man even in the temperate zone possibly suffers generalized infections due to one or another fungus, in addition to the fungi that now are known to parasitize his skin, hair and nails.

These fungal infections, together with the opening field of antibiotics and the wide experience of our Armed Forces with mycotic conditions in the tropics, have served to stimulate much interest in mycology and already distinct advances have been made. Our chief lack of basic information in this field seems to be in the physiology of fungi, and we may look forward to developments in fundamental as well as in medical and industrial mycology.

To summarize, a few general remarks may be made. The basic science of Bacteriology is developing in many directions. There is no line of distinction between its various fields, nor between the diverse phases of the subject and other fields of science. Industrial and medical research in microbiology has been fundamental and abstract as well as applied, and, under whatever aegis, scientific advances have been mutually contributory. The distinction between so-called pure and applied science is fast fading if it has not indeed already disappeared.

Recent advances have contributed to another common principle, namely, the similarity of basic biological phenomena among the wide range of microscopic forms: metabolism in terms of enzymes and chemistry, cellular biology, chemical composition, parasitism, immunology, and reaction to external conditions.

If the two principal advances in Bacteriology were to be given, they might well be stated as the demonstration that scientific progress can best be made by a correlation of scientific approaches and the establishment of the common fundamental nature of the minute forms of life.

A REVIEW OR GASTROENTEROLOGY FOR 1945

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The literature on gastroenterology during 1945 was extensive. The various papers are particularly noteworthy because of the advances that have been made in diagnosis and treatment of many gastroenterological problems which arise in everyday practice. It is not my intention to include background on the subjects in this review because of the detail involved. The alimentary canal is usually discussed under separate headings, therefore it is deemed proper to group a summarical review in like manner.

ESOPHAGUS AND STOMACH

Esophageal varices have been shown to be much more common than was formerly suspected and are frequently the source of fatal hemorrhages. Patterson and Rouse (39) report a series of cases in which the varices were injected with a sclerosing solution even in the presence of hemorrhage. They maintain that only time will justify the conclusions drawn. It is their opinion that the results so far observed justify the procedure.

Clark (10) brings up the question of differential diagnosis between gastrointestinal conditions and cardiovascular disease. He points out that diaphagmatic hernia will frequently present a clinical picture resembling heart disease, particularly angina. He emphasizes that the symptoms of hiatus hernia are more apt to be associated with eating than with effort, and the pain is less promptly relieved with nitrates. He reminds us that gallbladder disease very frequently is found in association with coronary heart disease and in some instances the gallbladder will initiate attacks of angina. It is his belief that in selected cases the cholecystectomy may lessen or even clear up the attacks of angina. Feros (15) has presented an interesting study on the electro-cardiogastrographic test and its possibilities in differentiating various gastric changes. He points out the possibilities it offers in differentiating benign and malignant lesions in the stomach. It has been stated that the intra-gastric electrical conductibility can be influenced by changes in pH, changes in the gastric tissue and by general modifications of the total organism. Generally speaking Feros agrees with Bockus that a clinical evaluation of this procedure must await further study on a much larger group of cases. Others (26, 36, 46) in discussing the various diagnostic procedures in gastro-duodenal disease believe that the present methods of diagnosis are quite accurate with emphasis being placed on the history, x-ray, gastroscopy, gastric analysis and stool examination. Thorek (51) writes that in severe gastric disease involving the esophagus in which stability is a factor, gastrostomy should not be deferred until the patient's condition becomes critical. Too often the operation is considered only after the patient's condition is deteriorated by malnutrition and disease and at that time gastrostomy is attended by great operative risks and offers little benefit. Thorek believes that early operation tends to maintain nutrition and strength and frequently improves the condition of the esophagus by removing the irritation due to alimentation. In addition to this it may furnish information regarding the location and the nature of tumors in this region. One of the most important contributions that has been receiving considerable emphasis has been that of bilateral vagotomy for hypermotility and hypersecretion in gastric disease, particularly intractable ulcer. The supradiaphragmatic section of the vagus nerves, as described by Dragstedt and his associates (13, 52) conclusively shows that hypersecretion can be reduced and the motility likewise inhibited with marked clinical relief of the patient's symptoms. Roth and Ivy (19, 43) have

demonstrated experimentally that the stomach will still respond to caffein after bilateral section of the vagus nerves and they draw the conclusion that caffein presumably exerts its action peripherally on the gastric mucosa and not on a neurogenic basis. Gianelli and Bellaflore (17) have reported that an antiulcer factor called vitamin U has been shown to be effective in experimental peptic ulcer and they adopt the principle of giving their patients a liberal convalescent diet. This is of interest because of the recent advocation of the use of amino acids (32) and a high protein diet in the rapid therapy approach to ulcers. In addition to this, the use of tobacco was permitted. One of the newer drugs which has been described for use in hypermotility of the stomach is Dibutoline, which Peterson and Peterson (41) have shown is very similar to atropine and equally effective, but that the duration of action was shorter than for atropine. The advantage in using this new drug is that it has no cardiac effects and no mydriatic effect. They maintain that the margin of safety for this drug is very great and they have observed no idiosyncrasies. Ivy, Sandweiss and others (26, 45) present the interesting subject of the hormonal control of hypermotility and hypersection. Both of these groups have conclusively shown that there is an anti-ulcer factor contained in extracts from the intestinal mucosa, extracts of the urine of pregnant women and also certain pituitary factors. The active principle has been isolated and purified and they define the unit of the hormone to be that amount which will reduce by fifty percent the secretory response to one milligram of histamine in a twenty-pound dog with a pouch of the entire stomach. This has been found to be twenty milligrams of the active principle. It must be given intravenously because when other routes are used, for example, subcutaneously, the amount required is trebled.

LIVER AND GALL BLADDER

Two new tests for the determination of the presence of gallbladder disease have been described by Morrison and Swalm (34) which are predicated upon the determination of the specific gravity of the bile obtained from the liver and the gallbladder which in turn reflects their bile salt content. They observed that normally the specific gravity of gallbladder bile is greater than that of liver bile and in disease processes this ratio is disturbed. A new drug which offers some promise and has been marketed under the trade name Profenil has been described by Weiss (55) to be well tolerated and of low toxicity. It has been shown to abolish smooth muscle spasm irrespective of its origin, neurogenic or myogenic, and he predicts that in time it will replace papaverine and belladonna. The new drug may be given in tablet or hypodermic form.

Most of the gastroenterological literature for 1945 has been centered around the liver (5, 18, 23, 24, 25, 31, 40, 42, 48, 49, 56, 57) which deal with such conditions as amebic hepatitis and the necessity for early recognition particularly in those cases which develop pus and the rather prompt response which is obtained with emetine; infectious hepatitis and its relationship to homologous serum jaundice and post-vaccinal hepatitis. It has been shown, in regard to the latter three conditions, that one and the same factor are presumably concerned and the only difference is in the mode of transmission. One outstanding fact in regard to virus hepatitis is the necessity for prolonged bed rest and the question of recurrence following too early ambulation. Biopsy studies in many cases have shown the consistent finding of necrosis and in a very small percentage of cases have led eventually to cirrhosis. From a diagnostic standpoint the tendency has been to develop a series of rapid tests that can be done expediently and inexpensively (14, 18, 21, 33, 37, 38) the most notable of which have been the modification of the Harrison's test for bilirubin in the urine and the quantitative determination of the serum bilirubin according to the methods developed by Ducci and Watson (14). This latter test has its greatest value in the differential diagnosis between obstruc-

tive and toxic jaundice. The crux of the newer methods of technique and interpretation is based on the fact that the quantitative prompt bilirubin is low in toxic (hepatic) jaundice, and high in obstructive jaundice. Two new papers have appeared (1, 44) on the determination of vitamin A in liver disease and the utilization of a vitamin A test meal to show the hepatic response in health and disease. Aldersberg (1) and his associates maintain that the normal fasting level of vitamin A varies from 40 to 100 micrograms percent. In severe liver disease this falls to levels of 20 or 30 and following a test meal, normally peaks of up to 276 micrograms are reached, whereas in hepatic disease there is no response. An additional note in regard to Atabrine and its effects on the liver, Butt (8) states that the toxic effects from this drug are few and far between and that its use in malaria is relatively safe because of this fact. Bauer (3) points out that cholinesterase can be demonstrated in serum. He has found that in liver disease the values for this substance are markedly lowered and that it is a relatively sensitive test. Hines and Kessler (22) report that penicillin produced extensive hemorrhages in two of their patients who had received the drug for bacterial endocarditis and the cause is presumably that penicillin increases the sensitivity to heparin. Havens and Paul (20) demonstrated that the intramuscular injection of gamma globulin was effective in preventing the spread of infectious hepatitis. From a theraupetic standpoint Darmady (12) supports other authors (Wade, Jolliffe, Alpert and Barker, 2, 29, 53) in the rather generally accepted observation that large amounts of protein are of primary importance in the treatment of hepatitis as a result of infection and also cirrhosis due to any cause. In addition to the use of a high protein dietary supplement, Beams (4) has reported that choline and cystine are of great value in treating cirrhosis in the hypertrophic phase. Cartwright and Wintrobe (9) support Watson and Castle (54) that choline in the treatment of cirrhosis of the liver has no deleterious effect on the blood picture. In a study of a series of patients with pernicious anemia, Boyden and Layne (7) found that the incidence of gallbladder disease was higher in this type of case. Bennett (8) in discussing the possible etiological factors in the development of disturbed protein metabolism predicates the hypothesis that the responsible factor is an absence of the methyl group and its relation to the sulfur-containing amino acids. She summarizes the complex chemistry by saying that an adequate supply of preformed labile methyl groups is necessary for normal growth and that this methylation factor presumably is based upon bacterial flora in the bowel and the ability of the liver to make use of these various chemical compounds resulting therefrom.

INTESTINAL TRACT

Isaacs (27) states that until 1944 only 127 adenomas of the pancreas had been reported, and the fact that these patients must be differentiated from those having malignant tumors of the pancreas. He points out that the biggest difficulty is in locating the tumor and surgically removing it with a resultant excellent chance for complete recovery from the hyperinsulinism.

Darby, Jones and Johnson (11) report on the use of L. Casei factor in sprue and they propose that the group of substances related to L. Casei factor and folic acid be termed the vitamin M group. Kiefer and Ross (30) state that their experience with 102 cases of chronic ulcerative enteritis has been that conservative management is advisable in the acute forms of the disease, and also in the mild cases of chronic uncomplicated terminal ileitis. However as a general rule these authors state that in the chronic stage the best method of therapy is surgical resection. An interesting commentary by Most (35) to the civilian physician is his emphasis of the use of zinc sulfate flotation of stool specimens as a practical and efficient method of detecting the majority of the various intestinal parasites, particularly those found in persons who have been in the armed services and are returning to this country from military duty. Smith (47) in discussing Shiga dysentery points

out that a diagnosis by proctoscopy is possible within twenty-four hours after the onset of symptoms. In his series of cases 47 percent had negative stool cultures and the diagnosis might have been missed if direct visualization of the colon had not been done. He emphasizes that the golden opportunity for effective treatment occurs in the first twenty-four hours and that at this time the diagnosis can only be made in many instances by proctoscopy. Sokoloff (50) reports that chronic amebic infection responds very satisfactorily to anhydrous lactic acid and in some instances better results are obtained when combined with iodine.

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RECENT ADVANCES IN PHARMACOLOGY AND MATERIA MEDICA

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Any brief report on the present status of pharmacology involves the careful selection of those topics which seem to be of major importance, and even these must be treated somewhat cursorily. I have, therefore, chosen to divide this report into two sections; the first dealing with the present status of, and the future outlook for, the chemotherapy of infectious diseases, and in the second section to discuss miscellaneous advances in divergent areas.

In dealing with the present status of chemotherapy, the discussion can be conveniently divided into two phases: (1) the sulfonamides, and (2) the ever-increasing group of substances derived from living organisms and ambiguously called "antibiotics." Of the ten or twelve clinically useful sulfonamides which have been developed over the last ten years, it seems safe to say that at the present time only one of these—sulfadiazine—need be given serious consideration. It is generally recognized that when a sulfonamide is indicated sulfadiazine should be the drug of choice. The only serious exception to this general statement would be in the case of those sulfonamides, represented by sulfasuxidine, which are not absorbed, and which have a certain limited usefulness through their local action in the gastro-intestinal tract.

There have been no new developments in the case of sulfadiazine, but certain factors involved in its clinical application have become more clearly defined. Among these, the following are worthy of note:

(1) Clinical effectiveness following systemic administration is equal or superior to that following local application.

(2) The efficiency of sulfadiazine prophylaxis has been definitely established, particularly in those diseases caused by the hemolytic streptococcus. Prophylactic use must, however, be balanced against:

(3) The increasing incidence of patient sensitivity to the drug and the development of strains of sulfonamide-resistant organisms;

(4) And finally, it seems possible to predict, on the basis of physico-chemical studies, that other substitutions of the basic sulfonamide nucleus will not produce drugs which will have any greater therapeutic effectiveness than does sulfadiazine.

Available data in the field of antibiotic research are undoubtedly incomplete, but it seems certain that some 50 to 75 antibiotic substances have been partially or completely isolated and are in various stages of investigation; however, only two—penicillin and streptomycin—can be said, at present, to have widespread clinical importance.

Penicillin is now available in adequate quantities, although the supply is not unlimited and precludes, for the time being at least, any widespread application of unproven methods of administration. The concensus among clinical investigators is that for maximum effectiveness penicillin must be administered parenterally. There is, as yet, too little clear-cut experimental or clinical evidence to enable one to predict the possibilities for the oral administration of penicillin. Herein lies a major difficulty in penicillin therapy. In most instances, the physician will feel that the patient must be hospitalized before he is given penicillin. This is to insure the all-important factor of maintaining adequate blood levels by means of controlled day-and-night administration. The choice between sulfadiazine and penicillin in the management of disease produced by susceptible organisms is, of course, determined primarily by the susceptibility of the organism in question to

each drug. Where either drug will satisfactorily combat a given organism the choice frequently hinges on the difficulties encountered in administering penicillin.

The special cases of syphilis and gonorrhea require separate mention. It must be emphasized that the use of penicillin the therapy of syphilis is as yet in the experimental stage, and will retain that status until sufficient time (2–5 years) has elapsed to permit the proper evaluation of results. It is not possible to state definitely whether penicillin alone or in combination with heavy metals will significantly advance the therapy of this disease. In the case of gonorrhea two factors must be recognized. The first of these is the extraordinary susceptibility of the gonococcus to many forms of therapy, and its equally extraordinary ability to develop resistance to any given therapeutic agent. Penicillin-resistent strains of gonococci have been reported, and it is as yet too early to predict the final status of this agent in the therapy of gonorrhea.

The second factor which must be recognized is the possibility of the simultaneous occurrence of gonorrheal and syphilitic infection with the latter in its innocuous primary stage being masked by the earlier clinical onset of gonorrhea. Under such circumstances, superficial healing of the unrecognized primary chancre may occur with the dosage of penicillin used to treat gonorrhea. This quantity of penicillin is grossly inadequate to ensure the destruction of all the spirochaetes and the patient is thus exposed to the possibility of developing treatment-resistant syphilis and to the hazards accompanying the inadequate treatment of this disease.

The clinical usefulness of streptomycin is still in the process of evaluation. The quantities available at present are too small to permit extensive controlled investigation. In general, streptomycin is effective against many gram-negative bacilli, whereas penicillin is ineffective, and the sulfonamides have only limited usefulness in infections caused by these organisms. The effect of streptomycin in controlling three diseases—brucellosis, tularemia, and typhoid fever—hitherto unaffected by chemotherapeutic agents has received considerable attention recently. At the present time the outlook for its usefulness in the treatment of tularemia is good; in combatting brucellosis, less than fair, and for typhoid fever, poor.

Even less can be said about the effectiveness of streptomycin, or any other chemo-therapeutic agent for that matter, in the treatment of tuberculosis. At the present time no optimism is justifiable.

No report of the present status in the field of chemotherapy would be complete without mention of the enormous possibilities which have been opened to investigators by the elucidation of the mechanisms of action of the agents just discussed. All of them are effective by virtue of the fact that they interfere with some essential metabolic activity of the organism. The application of this basic principle renders possibilities for the control of infectious agents virtually unlimited.

Of the host of advances which have been, or are being, made in other areas, time permits the mention of only three:

Thiouracil—This synthetic pyrimidine derivative possesses the unique property of inhibiting, in a manner not entirely clear, the production of the thyroid hormone. This activity had led to the use of thiouracil in the control of hyperthyroidism. However, its place in the general management of hyperthyroid patient has not yet been satisfactorily evaluated. It seems clear at the present time that thiouracil may not be depended upon to control completely such a patient, but that it must be used in conjunction with other procedures, including surgery. Its use is attended by a fairly high incidence of toxic reactions, the most alarming of which is agranulocytosis. This toxicity could conceivably lead to its abandonment as a therapeutic agent, but only time and wider clinical experience will determine this possibility.

Benadryl—It is a well recognized fact that histamine plays a very large part in the production of those lesions which characterize allergic reactions of all kinds. A long-held theory has supposed that if some substance could be found which

would antagonize the action of histamine it should be possible to relieve or prevent the manifestations of allergic disturbances. Benadryl seems to be such a compound. It is by no means a panacea for all types of allergic disturbances, but it seems to be outstandingly effective in providing symptomatic relief in angioneurotic edema, allergic rhinitis, and allergic bronchospasm. The drug does not affect antigen-antibody relationships or formation, and in this respect represents a purely symptomatic approach to a very complex problem.

Digitalis—It would be misleading to confine a review of recent advances to new drugs exclusively. Both clinical and experimental pharmacologists devote a large share of their time and effort to the improvement of therapeutic agents of known values. The gain which has been made in the direction of a more complete understanding of the chemical characteristics, the mechanism of action, and the rational clinical application of the digitalis bodies represents an outstanding example of this type of continuing progress. Until very recently the infinite complexity of digitalis in all its relationships has made the crude leaf the preparation of choice, and the oral route the only reliable method of administration. There is now, however, reason to believe that the limitations and uncertainties imposed by this combination may be overcome. More refined chemical techniques and more accurate and detailed pharmacological observations have resulted in the isolation, identification, and use of the active glycosides of digitalis in pure, unaltered form. Two of these compounds, digitoxin and digilanid C, are especially worthy of mention. They are receiving widespread clinical trial, and the reports on their effectiveness are very encouraging. This trend, supported by continually accumulating data, permits the prediction that the pure glycosides may eventually supplant the crude leaf, and it is very probable that their use will materially enhance our ability to control cardiac failure and, at the same time, increase our knowledge of the abnormal physiology of the failing heart.

RECENT ADVANCES IN AVIATION MEDICINE

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In any attempt to review recent advances in Aviation Medicine, one must remember that almost all aviation medicine is recent. Although a not inconsiderable amount of experimental work was done during the first World War, nearly all of this work was discontinued shortly after 1918, and much of the material that had been studied and investigated was forgotten.

In marked contrast to the policy followed in Germany and Russia, where the subject of aviation medicine was continuously and actively investigated, this subject was completely neglected in the United States. Therefore our entry in the late war made it necessary for us to establish a multitude of laboratories and to carry on our investigations with almost feverish haste in order that we should not be hopelessly outdistanced by the Axis.

In a brief review such as this, it is obviously impossible to adequately cover the entire field. I have, therefore, somewhat arbitrarily selected three different sub fields in each of which outstanding results have been reported during the past year or two.

First, I want to take up the subject of angular acceleration or centrifugal force. If a fighter pilot is diving at the rate of 450 miles an hour and pulls out of this dive on the arc of a circle having a radius of about one-half mile, centrifugal force will press his body down onto the seat of the plane with a force which will be slightly more than five times the force of gravity. Thus if the flyer's weight is 180 lbs., the

force of his body against the seat of the plane would equal more than 900 lbs. His arms would be so heavy that he would be unable to lift them. The blood would have a weight five times its normal value. This would make it difficult for the heart to pump an adequate amount of blood to the brain. Blood would, therefore, tend to drain out of the upper part of the body and become pooled in the abdomen and the legs, and the aviator would suffer from cerebral ischemia. The first effect of this ischemia would be a blurring and graying of the vision as though a semi-transparent curtain were lowered before the eyes. This would be accompanied by a narrowing of the visual field. If the centrifugal force on the body is continued or increased, the aviator will "black out," that is, he will suffer a complete loss of vision and finally will lose consciousness. The extent of the physiological changes produced depends upon both the magnitude and duration of the centrifugal force applied to the body. Most young normal individuals can tolerate a centrifugal force as great as four to five G. for a period of as long as five to ten seconds.

One of the problems of aviation medicine has been the development of devices for protection of aviators against these effects of centrifugal force. So far the most successful device of this sort developed is the so-called arterial occlusion suit, of which you have probably read in the newspapers. This consists of a suit into which are incorporated three inflatable elastic bandages; one across the abdomen and one around each of the thighs. When the aviator performs any manuever which involves increased centrifugal force, these bandages are automatically inflated in such a way that pressure is exerted on the wall of the abdomen and on the large arteries in the thighs. This pressure constricts or occludes these arteries, with the result that the blood is prevented from pooling in these parts. This means that more blood is retained in the upper part of the body and the aviator's tolerance of centrifugal force is increased. However, there is a definite limit to human tolerance of centrifugal force even with the best protective devices. This limit is on the average about 7 G.

The second development which I wish to discuss is the equipment for what is known as pressure breathing. It is well known that at altitudes of more than 15,000 feet men find it difficult or impossible to live and carry on ordinary activities because of oxygen lack. This lack of oxygen is not the result of any decreases in the percentage of this gas in the air, but rather of a lowering of the oxygen tension as a result of the decrease in total barometric pressure. It is quite obvious that protection against this anoxia of altitude can be obtained by breathing oxygen enriched air. Thus a person breathing 100 per cent oxygen at an altitude of 35,000 feet, where the barometric pressure is a little less than 100 mm. Hg. would be just as well off in regard to his oxygen supply as though he were breathing air at ground level. However, if he goes up to 40,000 feet, even breathing 100 per cent oxygen the alveolar oxygen tension would drop to about 55 mm. Hg. and his arterial oxygen saturation would be down to something under 80 per cent. He would, therefore, be in a precarious situation and on the verge of losing consciousness. It is generally stated that 42,000 feet is the absolute ceiling for the most resistant aviator, even when he is breathing 100 per cent oxygen.

During the latter part of the war, oxygen equipment was developed which delivered oxygen to the lungs of the aviator at a pressure of slightly greater than that of the ambient atmosphere. This results in an increased alveolar oxygen tension and makes it possible for the aviator to go a few hundred feet higher than he would otherwise be able to do. Two sorts of pressure breathing equipment have been developed: first, the constant pressure type in which the increased pressure is maintained continuously and second, the intermittent type in which the increased pressure is applied only during inhalation. Breathing is a little easier with this type of apparatus, but it is more complicated and therefore more likely to get out of order.

And now we come to the pressurized cabin and the problem of explosive decom-

pression. Even before the war the pressurized cabin was beginning to come into use as a means of protecting passengers in aircraft against the unpleasant effects of decreased barometric pressure. This mechanical development was carried to a much higher state of perfection during the war and as everyone knows, was a not inconsiderable factor in the success of our long distance, high altitude bombers. The pressurized cabin, of course, is the ideal solution to many of the problems of high altitude flying. But as is so often the case, the solution of one problem pushes to the forefront other as yet unsolved problems. Thus with the pressurized cabin in common use, the problem of explosive decompression became one of paramount importance. If a bomber is flying at an altitude of 35,000 feet where the barometric pressure is 180 mm. Hg., with the pressure inside the cabin at 560 mm. Hg., the crew would be subject to the hazard of an extremely rapid drop in barometric pressure in case of a large caliber shell piercing the cabin. Under these circumstances, the barometric pressure in the cabin might drop as much as 380 mm. Hg. (one-half atmosphere) in a fraction of a second. This is a pressure change of 7½ lbs. per square inch. At first thought one would be inclined to feel that human beings could not tolerate such rapid and extensive changes in barometric pressure. In the early days of the war, explosive decompression was considered an extremely serious hazard. It became necessary that we should know what the tolerance of human beings was to such rapid changes in pressure and also what harmful effects might be expected to result. Here in our Ohio State laboratory, we began investigating these problems in January, 1942. We developed a technique for producing explosive decompressions at a rate which was equivalent to going from ground level to 50,000 feet in .02 of a second. Various species of animals were subjected to such explosive decompressions and to our surprise there were no harmful effects. A few minor hemorrhages of the lungs and occasional small hemorrhages in the ventricle of the brain were the most serious effects produced. None of these was of such a nature as to seriously incapacitate the animal. In fact, experimental animals showed complete recovery from such minor lesions in a period of two or three days. The only serious hazard seemed to be the possibility of the extreme expansion of the gas trapped in the stomach and intestine. At 40,000 feet, a gas would occupy a volume five times as great as that occupied at ground level. This means, of course, that when the gas is trapped in a confined space in the body, considerable pressure might be developed. We found that herbivorous animals, such as guinea pigs and rabbits, that are known to have considerable amounts of gas in the gastrointestinal tract, occasionally died following explosive decompression as a result of ruptured stomachs. In no case, however, did any of the dogs or cats which we used suffer serious injuries from explosive decompression.

We investigated in some detail the physiological effects of such rapid changes in barometric pressure. As would be expected, we found that there was a momentary but rather marked increase in the intrathoracic pressure. This is, of course, caused by the fact that the expanding air in the lungs is unable to escape through the trachea at a rate sufficient to keep pace with the fall in the ambient pressure. In other words, the lungs decompress at a slower rate than does the experimental chamber or the cabin of the aircraft. This rise in intrathoracic pressure is, we believe, the fundamental cause of all other physiological changes that take place following explosive decompression. Among these effects is a rise in the cerebrospinal fluid pressure. While our experiments on this point cannot as yet be considered final, such data as we have seem to indicate that the rise in cerebrospinal fluid pressure parallels, both in extent and duration, the rise in intrathoracic pressure. We also found a marked slowing of the heart and a drop in blood pressure. The slowing of the heart occurs immediately following the explosion. The drop in blood pressure begins after a delay of perhaps a second or so. This drop in blood pressure is probably due, at least in part, to interference with the venous

return to the heart by the increased intrathoracic pressure. There are also undoubtedly reflexes involved. Cardiac slowing seems to be solely of reflex origin since it is abolished by bilateral vagotomy. Our work on animals was followed by many experiments with human subjects. In general these experiments verified the results which we had previously attained with animals, although of course there were many things that we had done with animals that it was impossible to do with men. Furthermore we have never subjected our human subjects to the extremely rapid decompressions used with animals. We have shown, however, that explosive decompression is not a serious hazard to aviators.

In this short paper I have not attempted to give credit either to individuals or to laboratories for developments which I have mentioned. They were all cooperative undertakings in which a number of laboratories participated. It must also be borne in mind that there have been many other developments which were no less important than those I have discussed, but time does not permit further elaboration of the subject.

RECENT ADVANCES IN PHYSICAL MEDICINE

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The field of physical medicine is expanding very rapidly and with such development is demonstrating its value in a broad and neglected phase of medicine as practiced today.

The Council on Physical Medicine of the American Medical Association defines physical medicine as including the employment of the physical and other effective properties of light, heat, cold, water, electricity, massage, manipulation, exercises and mechanical devices for physical and occupational therapy in the diagnosis and treatment of disease.

Physical Medicine is developing and progressing into three major fields: (1) physical therapy and the employment of physical agents in diagnosis, (2) occupational therapy with the usual arts and crafts plus the wider field of pre-vocational, avocational, and vocational pursuits, and (3) reconditioning of the convalescent patient which includes not only physical training but also the provision of educational and recreational programs as developed by our military services during this past world war to utilize the period between definite care and ability to return to productive work; thus shortening convalescence and obtaining maximal functional recovery.

In 1944 the Baruch Committee on Physical Medicine was initiated by the grant of Bernard M. Baruch to advance and encourage research, teaching and training in the field of physical medicine. The general research and training projects were formulated as follows:

(1) To develop both medical and technical teachers of physical medicine in the basic sciences and clinical aspects of physical medicine.

(2) To investigate the problems of hydrology, climatology and spa therapy.

(3) To study the prevention and manipulative aspects of the structural mechanics of the human body.

(4) To study and develop electronics and other physical agents because of their increasing importance in physical equipment which could be employed in research as well as in clinical application of physical medicine.

(5) To promote special clinical investigation of the psychologic and psychiatric aspects of physical medicine.

During the past year, grants were made to a number of medical schools and Dr. Frank H. Krusen, medical director of the Baruch Committee, has summarized the projects at the specific institutions as follows:

(1) Columbia University, College of Physicians and Surgeons—Research projects dealing with insulin therapy in combination with fever therapy produced by physical means; studies of electric shock therapy; the effect of temperature on hemorrhage, fluid, and electrolyte balance; distribution of volume of blood, and metabolic disturbances resulting from circulatory changes; basic problems of circulation in small vessels and capillaries; the use of radioactive isotropes in circulation investigations.

(2) Medical College of Virginia—Study of birefringence of mammalian muscles; changes in muscle proteins during atrophy; use of electrical stimulation, massage or baths to overcome atrophy.

(3) Massachusetts Institute of Technology—Investigation of the dielectric properties of muscles and tissues in high frequency fields and nerve impulses by electronic methods.

(4) Harvard University—Study of biochemical factors relating to fatigue and the psychiatric aspects of fatigue in psychoneurotic patients.

(5) University of Southern California—The evaluation of compensatory action in muscles or muscle groups; the use of soft tissue x-rays and metal pin implants to study muscle movement; the determination of electrical potentials in muscular contractions; the interruption of neuromuscular pathways by pressure, nerve section and chemicals; the effects of internal environment on regeneration of neuromuscular pathways and return of function.

(6) University of Iowa—Research in the use of thermogenic agents on deep tissue heating, and the effects on circulation of short wave diathermy in animal experiments.

(7) Marquette University—The effects of temperature changes on the neuromuscular apparatus with special reference to thermal shock.

(8) Washington University—Research program on body mechanics.

Laboratory research in electrodiagnosis, electromyography, and low frequency muscle stimulation has been a prominent investigative field.

In studies on peripheral nerve lesions, electrodiagnosis by means of a progressive current of long duration has shown great prognostic importance. A progressive current is one which increases with time and in peripheral nerve lesions, there is a progressive diminution in threshold amperage until the period of denervation is reached. With recovery, there is a rise in threshold amperage. These electrical signs of recovery precede clinical evidence of motor and sensory recovery often by months.

In a like manner, electromyography is of diagnostic aid in similar peripheral nerve lesions. No electrical activity can be recorded from normal relaxed voluntary muscle, although it is always present when there is action in muscle tissue. In practically denervated muscles, fibrillation action potentials can be obtained. During re-innervation, fibrillation action potentials decrease. In detecting small degrees of nerve interruption, electromyography is of particular value. It also helps in placing the level and extent of lower motor neuron lesions since the amount of denervation can be assessed. Thus work in electrophysiology and electropathology has resulted in the recording by suitable needle electrodes, the action potentials of muscles. To date such methods are chiefly used in laboratory studies but a definite clinical use is in the making.

The relation of Physical Medicine to Psychosomatic Medicine has been emphasized in the use of electric shock therapy in the various psychoses. Electric shock is the most easily administered shock therapy and the results are comparable to those of insulin and metrazol. As in other forms of shock therapy, only the existing mental state is altered. There is no change in the prepsychotic personality and other forms of psychotherapy are essential.

The combination of physical and drug therapy in the forms of fever-chemotherapy and of ion transfer has developed further.

Studies have been continued in the use of artificial fever and chemotherapy in early syphilis in the hope to obviate the necessity of long courses of either chemotherapy or of fever-chemotherapy. Valuable data has been obtained on such combinations during this past World War.

Ion transfer with histamine and novocain has been used extensively in recent years. Irritation of the skin and underlying parts has been used more or less successfully in the treatment of aches and pains due to soft tissue involvement. Pronounced analgesic action is probable directly due to improved circulation which relieves tension in subfascial spaces and removes toxic products. Histamine ion transfer is one of the simplest and most effective counterirritant measures available. In cases of painful limited joint motion, novocain ion transfer is very effective with complete relief of symptoms plus surface analgesia for three to four hours.

Continued studies using hypotheramy further corroborated its uses for surgical anesthesia, preservation of poorly nourished tissues, treatment of infection and shock, and treatment of burns. Preliminary observations on selective destruction of superficial tumors by temporary local asphyxia using carbon dioxide ice have proven the feasibility of this method.

Ultraviolet irradiation plus the use of fluorescein has been used with success in determining the viability of strangulated intestine as well as in the establishment of diagnosis and prognosis in peripheral vascular diseases. When fluorescein is injected intravenously, it can be made visible by a beam of ultraviolet radiation on reaching any area of exposed skin or mucous membrane by the blood stream. In cases of damaged bowel, the presence of fluorescence has been shown to be sufficient evidence of viability. The postoperative course and pathologic sections have borne out the prognosis based on this method and so has removed the usual uncertainty incidental to such cases.

For years there has been a need for a means of estimating heat radiation in clinical practice. Recently there has been developed an experimental instrument, a thermoradiometer, which can be placed in the patient's skin and directly measure the radiation flux. It is hoped that a simple clinical recording instrument that will allow more accurate estimate of administering heat radiation will be an outgrowth of these experiments.

Laboratory experimentation with microwaves and supersonics as well as with the cyclotron and atomic energy have indicated that it is within the range of definite possibility that the therapeutic use of these powerful new forms of physical energy may bring far-reaching developments. Radioactive sodium as prepared by means of the cyclotron has already been used as a tracer substance in the blood in the study of patients with peripheral vascular disease. Thus the past few years have shown progressive advances of sound large scale developments in physical medicine.

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RECENT ADVANCES IN MEDICAL GENETICS

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The most spectacular, if not the most important advance in medical genetics in recent years has been the unraveling of the complexities of the blood agglutinogens. Fourteen such agglutinogens are now known, and a fifteenth is postulated and will doubtless soon be described. These antigens in various combinations form the so-called human blood groups and types. Not many years ago we spoke of four blood groups. Today we know 5,760, and we will soon be able to distinguish 8,640, when the last of the three Hr antigens is identified.

The various medical and medico-legal problems centering around the blood groups are fundamentally problems of medical genetics, and can be solved only by modern medical genetic methods. The individual agglutinogens are inherited as dominant factors, some of them related as alleles of a series, others independent of each other in inheritance. In the A–B series there are now eight groups, by virtue of three sorts of A antigen. They are as follows: O, A^1, A^2, A^3, B. A^1B, A^2B, A^3B. In the M–N series there are five types, namely, M, N^1, N^2, MN^1, MN^2. Since any one of the eight in the A–B series could be any one of the five in the M–N series, there are 8×5, or 40 groups in these two series combined. In the P. series there are four types, P^1, P^2, P^1P^2, and P−. This makes 40×4, or 160 groups. Since any one of these may contain antigens in water-soluble form (secretors) or in alcohol-soluble form (non-secretors), there are now 160×2, 320 groups. The recently-discovered Rh antigens are combined into eight types, Rh°, Rh′, Rh″, Th°′, Rh°″, Rh′ ″, Rh°′ ″ and Rh−. These, added to the list, make 320×8, or 2,560.

The newest of the agglutinogens are the Hr factors. These are not independent of the Rh antigens, but are reciprocally related to them, so that we must redescribe the Rh group by adding an Hr designation to them. At present we can identify Hr′ and Hr″, and no doubt soon will have identified Hr°. Using all three Hr factors, there are 27 Rh–Hr groups. Multiplying these 27 by the 320 groups which we identified without the Rh–Hr antigens, we have 320×27, or 8,640 human blood groups.

These groups are all of use in medico-legal cases of disputed paternity, and in the identification of individuals, but only the A–B series and the Rh–Hr series are of practical importance in transfusions. The A–B groups are involved in transfusions because certain individuals contain natural antibodies against agglutinogens A and B. The Rh–Hr groups are of importance for another reason, for, although no natural antibodies against these antigens are ever present as far as we know, antibodies can be produced against them when they reach the blood stream of a person lacking them. Thus in multiple transfusions Rh− blood must be given to an Rh− person.

The most important application of the Rh antigens is in pregnancies where an Rh− woman caries an Rh+ fetus. Here the antigen of the fetus may pass through the placenta into the mother, immunizing the mother. The resulting antibodies may return through the placenta and unite with the Rh antigen of the embryo, causing one or another of the manifestations of erythroblestosis (Levine, 1943; Wiener, 1943, 1945).

The Rh antigen of the embryo is of course inherited from the father in these cases. The father is, therefore, Rh+. He may be homozygous (pure) for the Rh factor, or he may be heterozygous and carry the gene for Rh−. In the first instance all his children will be Rh+, in the second, only half. As a rule the first Rh+ pregnancy serves merely to immunize the mother, while a second or later Rh+ pregnancy stimulates the further rapid production of antibodies, which may then affect the embryo. Occasionally a first Rh+ child is affected, and we have some evidence in our laboratory that these affected first-born children show spina bifida and other gross abnormalities. In some instances affected first-born children may be the result of a previous transfusion given to the mother.

When we determine by genetic methods how often by chance an Rh− woman would be expected to marry an Rh+ man and to produce an Rh+ child, we run into some interesting facts. In a population such as that of the United States we would expect 28.8% of all children born to have one or another Rh antigen which the mother does not have. If all such cases are potentially erythroblastotic, we should expect the incidence of erythroblastosis to be 28.8%. However, the frequency of clinically diagnosed cases has never approached this figure. The recorded incidence is about one in 200 births, or about one-half of one percent. Obviously the difference between 28.8% and one-half of one percent is a discrepancy which must be explained.

First of all it has been observed that of the three Rh antigens, only Rh° is of any great importance in producing symptoms. There have been a very few cases reported of effects due to immunization with Rh′ or Rh″, but the number is relatively insignificant. We may confine our attention, then to Rh°. When we compute how often a child will be expected to have Rh° when the mother lacks it, we find the answer is 8.7%. This is much closer to the observed half of one percent, but still far enough away to demand further investigation.

Next we recall that first-born children are seldom affected. In our American population about 31% of children are first-born. Eliminating these from our calculations, we would expect 6% of children to have Rh°, to be born of mothers lacking Rh°, and to be second- or later-born in the family. This further closes the gap between the expected and the observed incidence of symptoms due to Rh immunization, but still leaves a discrepancy.

Looking further, we see that the cases of erythroblastosis are not distributed randomly among the Rh− mothers, but are grouped into specific families. This suggests that the Rh° antigen may permeate the placenta only in certain Rh− mothers, or that perhaps only certain Rh− women are capable of producing potent antibodies. It may be that both these things account for the fact that not as many cases of erythroblastosis are found as can potentially occur.

Another intriguing possibility suggests itself, and the exploration of this possi-

bility has led to suggestive results. It is conceivable that in some instances where the antigen immunizes the mother, and the antibody in turn reaches the fetal circulation, that the effects on the fetus are different from those usually recognized as classical erythroblastosis.

Following the lead of Yannett and Liebermann, we have investigated the possibility that Rh immunization might in some instances result in feeble-mindedness. Our results confirm this, and we tentatively suggest that this finding raises the incidence of effects from one-half of one percent to one percent, thus closing the gap further.

Still another genetic factor may be involved in the recent discovery by Wiener that immunization may result in either of two kinds of antibodies, univalent or bivalent. The manifestations may depend upon the kind of antibody produced.

In addition to the practical applications of the blood agglutinogens, which have taken up an undue proportion of this review, applications in prevention, in diagnosis, and in genetic prognosis have developed from modern medical genetic research. For examples of these, see Snyder, 1946.

Fundamental research on which such practical applications are built has progressed rapidly in recent years. The basic relations of the mutant gene in man have been thoroughly investigated. A new type of hereditary transmission, incomplete sex-linkage, has been added to the longer-known types (Haldane, 1942), and this has made possible the first chromosome maps for man.

Recent studies with the electroencephalograph by Lennox and his co-workers have shown that cerebral dysrhythmia is inherited as a dominant factor, and may be used in predicting the occurrence of epilepsy in families. The genetic aspects of human cancer have been thoroughly reviewed and documented by Blank (1944).

The biochemistry of several human anomalies has been worked out, and tied in with genic action. Thus a single gene controls the production of an enzyme which, when present, brings about a certain reaction, but when absent, fails to bring about the reaction. Mutations in single genes thus bring about, through failure to produce the appropriate enzyme, albinism, phenylketonuria, alcaptonuria, Von Gierke's disease, and other errors of metabolism. The enzyme, its point of action, and its genetic determiner can now be exactly specified (Haldane, 1942; Beadle, 1945).

Lethal factors have been investigated, and various rare human anomalies which were long thought to be simple dominant factors have been shown to be lethal in the homozygous condition (cf. Snyder and Doan, 1944). These dyscrasias include telangiectasia, minor brachydactyly, sebaceous cysts, spina bifida and Pelger's anomaly.

For a comprehensive review of the recent advances in fundamental research underlying medical genetics, see Muller, Little and Snyder (1946). For text books on medical genetics, there are recent editions available by Roberts (1940), Davenport, Keeler, Slye and Macklin (1940), Snyder (1941), Ford (1942), Gates, Snyder and Hooton (1943) and Bauer (1945).

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THE HAZARDS OF TROPICAL DISEASES AS A RESULT OF WORLD WAR II

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Serious consideration was given throughout the war to risks of introducing exotic diseases and other harmful agents into the United States through the traffic of war and the return of military personnel from abroad. Estimates of hazard varied widely, but the most critical epidemiological analyses anticipated little risk in most instances. This was the viewpoint also of the Interdepartmental Quarantine Commission jointly established by the Secretaries of War and Navy and the Administrator of the Federal Security Agency to study this problem. Precautions recommended by the Commission were established in special quarantine programs of the Armed Forces.

With the end of fighting and return of the bulk of combat forces, it is now possible to review actual results on a preliminary basis. Optomistic conclusions appear warranted though tentative. No acute outbreak or secondary spread of non-indigenous disease has been reported to date in the United States and while more slowly evident infections may yet be identified it must be remembered that traffic and return have now gone on for four years.[1]

Malaria has always received priority consideration among risks to the public health of this country as a result of the war. Aiming primarily at maintenance of fighting efficiency, the Army and Navy greatly emphasized prevention and suppression of this disease. Though malaria remained the commonest infectious disease of troops abroad, the 460,000-odd reported hospitalizations of Army

[1]Subsequent information requires revision of this statement. One soldier who arrived in San Francisco by air in patient status for neuropsychiatric disease on 28 December, 1945, in the incubationary stage of smallpox is considered the starting point of infection for six subsequent civilian cases. The mode of first secondary infection is uncertain but apparently indirect. Two other military cases arrived at this port in patient status because of smallpox on 29 March and 8 April, 1946; no apparent secondary infections occurred. In Seattle a diagnosed case of smallpox entered in patient status on 5 February, 1946, and was hospitalized immediately. The first secondary case was a patient in that hospital, vaccinated on 6 February with a primary reaction, whose smallpox began on 16 February. Most of the remainder of 40 cases which occurred in Seattle seemed traceable to this second person; routes of infection in the remainder were uncertain. In Los Angeles a diagnosed case of smallpox entered 28 January, in patient status; no secondary infection occurred. A Customs official in San Diego was diagnosed as having smallpox about 5 March, 1946; no definite source was determined and secondary cases did not occur.

personnel from the onset of war through December, 1945, are far below pessimistic anticipation. As this figure includes both initial and recurrent infections, the total of persons involved was appreciably smaller.

Malaria is not susceptible to practicable border quarantine, and prolonged detention of returning personnel in segregation areas to avoid dissemination of the infection among the general populace was deemed unfeasible and unnecessary. Considering that only a portion of persons infected abroad are liable to recurrence after return to the United States (about 60,000 military hospitalizations to 1, July, 1945) and that these will be diluted among the 130-odd millions in the country, often in non-malaria-supporting areas, it is evident little community risk is afforded. Multiples of this risk are offered annually by endemic malaria in the United States, and fears of exceptional virulence and resistance to treatment on the part of foreign strains have not been borne out. What risk does exist has been anticipated by the U. S. Public Health Service in extensive mosquito control projects in communities and about military installations in susceptible areas. Some returned military personnel will, of course, have recurrences of malaria, and local outbreaks may result as following previous wars, but these should remain minor and readily controllable by modern improved measures.

Historical experience indicated the general risk offered even in normal traffic by cholera, smallpox, plague, epidemic typhus, and yellow fever. Their special danger in war is a matter of record. These are the internationally quarantinable diseases, and safeguards established against them by international conventions recognize both their importance and their susceptibility to border quarantine techniques. Immunizations were employed against all of them by the Armed Forces along with water control, environmental sanitation, and disinfection and insect control by newly developed methods. These precautions were exercised even under combat conditions, as parts of preventive medicine toward combat efficiency. Results were evident. Smallpox occurring in the Army overseas was limited to 115 cases along with 64 of typhus and 13 of cholera through December, 1945. There were no cases of yellow fever or of plague.

Elaborate quarantine procedures in traffic to the United States were established by both Services, based on selective accomplishment of the above protective measures before departure from abroad. Only seven cases of smallpox have occurred to date in Army traffic to this country, and most of these arrived in patient status with full attention to contacts. It is possible but not clear that some secondary infection has occurred in Seattle and San Francisco.[1] One mild and atypical infection with typhus was recognized in himself by a medical officer on arrival in the United States after special work with the disease. Eleven typhus infections occurred among prisoners of war brought to the United States. No secondary cases developed, all prisoners having been disinfested before shipment and again inspected on arrival. It is apparent that risk of the quarantinable diseases has been negligible.[1] It may also be pointed out that several hundred cases of endemic smallpox are reported annually in the United States; twelve occurred among military personnel during the war.

Eight lepers were returned from Army personnel abroad in the past four years; all but one had a previous family history of the disease and none are considered contracted abroad, (nine others were detected before shipment overseas). Three Japanese and one Italian prisoner were leprous and were hospitalized during their entire stay. Had all these been new and unrecognized infections they would not have equalled the acknowledged risk in New York City alone.

Scrub typhus or tsutsugamushi disease has been reported in 6,800 cases. Other than one instance, no active infection has been recognized after return to the United States. This was to be expected from the short incubation period of the disease and the fact it is usually contracted in field exposure. Persons so occupied are not likely to return to this country suddenly. Nor are infected mites likely

to survive transportation in clothing or salvage in view of their fragility. Sandfly fever, of which some 12,000 cases were reported, is subject to similar limitations, and no cases have been recognized after return.

Dengue is sporadic in certain southern states and a handful of cases occurred there each year among troops. No case has been recognized among persons returning from overseas to the continent. Nevertheless, the disease did occur in Hawaii beginning in 1942, probably introduced by returnees from forward areas in the Pacific. Vigorous control was instituted in cooperation with Territorial authorities. The outbreak was well controlled, and no case has now been reported for several months.

Filariasis was much feared in some quarters early in the war, primarily as a hazard to troops themselves. All recognized cases were evacuated from endemic areas at once and slightly over 2,000 diagnoses have been made in the Army. None of these cases showed chronic elephantiasis which would be expected only from prolonged exposure and repeated infections. Microfilariae have been found in the blood with the greatest rarity. Even concentration techniques have routinely failed to show them, and risk to the general populace is obviously negligible.

Leishmaniasis has been diagnozed among hospital admissions 307 times including both cutaneous and visceral forms. No secondary cases have been reported. In view of the vigorous treatment accorded these infections and the necessity for all elements of an intermediate mechanism before transfer can occur, introduction of the disease into this country is most unlikely. The same pertains to relapsing fever, 220 cases of which have been reported almost evenly within and outside the United States. That it was predominately if not entirely tick-borne is suggested by the control of louse-infestation of troops, without which a different problem might have been presented. Self-limitation and fortunate susceptibility of the disease to therapy, and emphasis on control of lice and other insects among troops comprise the protection of our civilian population. Furthermore, relapsing fever, as mite typhus, is a disease of field conditions, and it is again improbable that persons recently exposed will often be returned within the incubation period. Once ill, they can be treated effectively before travel.

Future risk of all disease characteristically contracted under field conditions, will, of course, diminish with cessation of combat and with the advantages of essentially garrison life. This affects favorably the risk of all diseases so far considered, and of numerous others, especially the dysenteries and dermatoses.

Onchocerciasis, trypanosomiasis, Guinea-worm, and yaws have not been experienced in U. S. troops. In the last analysis the common illnesses abroad, including the tropics, are those which are common at home, and with the exception of combat injuries the same pertains to disabilities in war.

Schistosomiasis was contracted by some 1,200 men, mainly on Leyte, and for reasons already indicated additional significant numbers need not be expected hereafter, even among garrisons in infected areas. These cases have generally been mild, and because exposure was of limited duration the late cicatricial changes, which underlie the disability of indigenous cases, will probably rarely occur. For the same reason dissemination of ova should be infrequent, but principal protection of the homeland community will be afforded by its generally excellent sewage disposal. Furthermore, it has not been shown, despite intensive search, that any domestic snail is suitable for the life cycle of the oriental disease in the United States. In any event, risk from service personnel will probably not approach that associated with Shistosomiasis mansoni in imported farm labor from Puerto Rico.

Amoebiasis and bacillary dysenteries have occurred, too, but foreign strains have appeared no more virulent than those already widely disseminated in the United States. It has already become evident that chief protection against these diseases, including Ancylostomiasis, lies in well recognized and widely applied principles of waste and water care.

Approximately 20 soldiers have been diagnosed as having Japanese-B encephalitis. Considerable apprehension attached to this disease and the small number of cases to date is highly gratifying. Lack of established epidemiology is most impressive in evaluating risk to this country. Despite demonstration of mosquito vectors, the unknown rather then the known underlies our apprehension. This has been true of many diseases in history. Much comfort is gained from the proved preventive value of distance, small numbers of carriers, dilution, and continuing military alertness and medical care. Should significant outbreaks occur abroad, it is axiomatic that the full military program of preventive medicine will be applied, including probable immunization.

Much attention has been devoted by the Army and Navy to possible introduction into the United States of new species of vector insects. Disinfestation of aircraft was made a responsibility of flight personnel under supervision of the Medical Department and is routine at stations of take-off for this country. To date there is no evidence that any alien form has been implanted. It is possible this might not yet be apparent.

As previously stated, this report must be tentative. Nevertheless, favorable conclusions seem justified. Despite unprecedented breadth of travel and exposure, the military forces of this country in World War II have not subjected the United States to significant risk of disease from abroad. In many respects risk has been less than in normal prewar traffic.

This has not been the result of any single factor, but rather of the entirety of modern preventive medicine applied intensively by both Army and Navy. Exotic disease did occur and breaches of formal quarantine are acknowledged. But extensive investigation of likely hazards and critical application of preventive and corrective measures were effective in reducing risks to small proportions. This was undertaken first to preserve effectiveness of combat forces through protection of personnel in the field. Primary efforts were therefore directed to local risks and to men exposed to them. Measures included immunizations, protective clothing, insect repellents, water purification, waste disposal, mosquito and other insect control and additional environmental sanitation. The development and widespread adoption of suppressive medication and insecticides, and education of men and their officers to risks incurred were parts of this program. Quarantine precautions were established which took maximum advantage of the preventive care of the individual to assure safety to countries of entry. This was a re-orientation of quarantine procedure which is ordinarily directed at momentary observation when international borders are crossed. The military technique is fully applicable only when the responsible agency has control of the traffic throughout, but the principles involved should be of advantage in further development of international health measures.

Further protection has been afforded the United States after entry of military traffic. Thus personnel generally remain under military medical care for the duration of the important incubation periods, hospitalization has been available for the sick, and none have been returned to civilian status until maximum benefit has been offered. This has minimized risk to the patient and to his community.

A final link in protection of this country is the generally high level of sanitation, insect control, and medical care here available. Their continued assurance is a special responsibility of organized medicine. The total effect of the several factors herein discussed is a defense in depth based on broad application of preventive medicine, an essential field of medical science never so fully developed as during the recent war.

RECENT ADVANCES IN PATHOLOGY

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Research in the general and special fields of pathology during 1945 has been handicapped by World War II, with its great demand on manpower and the numerous pressing problems it put before the scientific minds of the nations at war. For this reason we find what little progress has been achieved in the fields of pathology nearly exclusively recorded in the North and South American literature. For the purpose of a better survey, the contributions which impressed the reviewer as "advances" in the fields of pathology will be discussed under the sections of: pathology of infectious diseases, intoxications, nutritional and metabolic disorders, circulatory disturbances, and diseases of unknown origin. Advances in the pathology of tumors, endocrine and nervous disorders are being reviewed by other members of the symposium in the medical science section and will be therefore omitted.

I. THE PATHOLOGY OF INFECTIOUS DISEASES

One of the most interesting contributions in this field seems to the reviewer a series of articles by Cavelti and Cavelti (1) on the pathogenesis of glomerulonephritis. They were able to produce in 127 out of 208 animals truly progressive lesions of glomerulonephritis by injecting a mixture of streptococci with homologous kidney antigen. Twenty-four animals died in the stage of acute glomerulonephritis; in 27 the glomerulonephritis went into a latent stage, and in 34 animals slowly progressive chronic glomerulonephritis was observed.

Another successful attempt to reproduce a frequently observed human infection in animals is reported by Clawson (2), who observed valvular lesions in rate after the intracardiac injection of Strep. viridens and Strep. hemolyticus. The lesions were not caused by the toxic effect of the organism, nor were they caused by an allergic reaction to the organism. Microscopically the lesions resembled closely those observed in acute rheumatic valvulitis in man.

The pathognomonic significance of the Masson body in rheumatic lesions of the lung were disputed by Herbut and Manges (3). From a study of 505 cases of unselected lung lesions over a period of 15 years, the authors concluded that Masson bodies represent intra-alveolar exudate in various stages of organization and are not specific for rheumatic fever or rheumatic pnuemonitis.

In continuation of their experiments on the relationship between swine brucellosis and human Hodgkin's disease, Brown, Forbus and Kerby (4) emphasized the similarity in the reactions produced in the lymph nodes of the hog by infection with the Brucella strain isolated from a human case of Hodgkin's disease and the strain naturally occurring in swine. On the other hand, they admitted that they have been unable to produce a disease entity comparable with human Hodgkin's disease.

In the field of fungus infections we find the interesting observation of Butt and Hoffman (5), who obtained close to 26% positive coccidioidin reactions in 700 cases admitted to the Santa Fe Coast Lines Hospital in Los Angeles. Autopsy of cases with positive skin tests revealed nodular fibrous lesions in which spherules and endospores of C. immitis were present in 45.4% of the cases with positive reactions.

The experiences of American doctors in the Pacific and African theaters of war gave rise to numerous contributions in the field of pathology in tropical diseases. As an example we may quote the study of Rifkin and Thompson (6) on the changes in early filariasis as observed in cases received from various islands in the South Pacific. The acute stage observed during the invasion of the parasite is mani-

fested by typical allergic reactions which are always local but may be also systemic. The subacute stage of infection is characterized by the development of granulation tissue in the lymphatic organs harboring the parasite. The chronic stage is characterized by nonspecific fibrous overgrowth in the areas of the degenerating parasites. The latter is then followed by lymph stasis and elephantiasis.

Also from the theater of the Pacific come our experiences with scrub typhus, or Tsutsugamushi disease. Allen and Spitz (7) compared the pathology of scrub typhus with that of other ricksettsia diseases. The focal encephalitis in scrub typhus and epidemic typhus can be well differentiated from the microinfarcts of Rocky Mountain spotted fever. Only slight vascular damage is found in scrub typhus in contrast to epidemic typhus. The authors believe that the fibrinoid degeneration of collagen, the necrotic changes in lymph nodes and spleen, and the acute diffuse glomerulonephritis are evidence of the action of allergens in ricksettsia diseases.

Numerous papers deal with the pathology of virus diseases. Pinkerton, Smiley and Anderson (8) studied the cytology of infantile giant cell pneumonia. They found cytoplasmic and nuclear inclusions which seemed identical with those seen in distemper infections of dogs and lower animals. This observation suggested to them a possible etiologic relationship between both diseases.

Lucas and Riser (9) studied the intranuclear inclusions found in the panleukopenia of cats. They found two types of granular nuclear inclusion bodies: clustered granular, and diffuse granular ones. Morphologically these inclusion bodies are identical with those found in the liver of yellow fever and severe burns, but the developmental cycle of the inclusion bodies seems a different one.

Lillie and Armstrong (10) studied the pathology of lymphocytic choriomeningitis in mice. If other routes of inoculation than the cerebral one were employed, the changes in the visceral organs were more striking. Fatty degeneration and focal necrosis of the liver, polyserositis of pleura and peritoneum, focal necrosis in thymus, spleen, lymph nodes and bone marrow were present in animals injected parenterally with the virus. From this study it appears probable that the spontaneous infections not using the intracerebral route of inoculation could produce visceral lesions more frequently, and that such lesions may well dominate the picture.

Saphir (11) reported the autopsy findings of 17 patients dying from poliomyelitis. In 10 cases diffuse lymphocytic myocarditis was present, in 6 cases interstitial pneumonia was found, in 5 bronchopneumonia. The author suggested that the myocarditis, which can only be detected by microscopic examination, may be responsible for the sudden death of some patients.

II. PATHOLOGY OF INTOXICATIONS AND TRAUMA

The interest of the pathologist in lesions encountered in various industrial occupations is evidenced by a series of articles in the field. Haythorn and Taylor (12) attempted to throw light upon the puzzling fact that in many cases patients with a considerable chemical silica content in their lungs did not show any clinical or pathological findings of the disease. Silica was extracted from silicotic lungs under careful preservation of the physical and chemical status and injected into rabbits and guinea pigs. Identical experimental lesions were obtained as with crystalline silica. These experiments proved to the authors that silica recovered from the lung has not lost any of its toxic properties by its "sojourn" through the body tissues.

In studying the effect of beryllium intoxication, Gardner and Heslington (13) produced atrophy of the spleen, progressive cirrhosis of the liver, and cortical sclerosis of the long bones, spines, and ribs. Seven rabbits surviving the injection of zinc beryllium silicate for seven months developed malignant osteosarcomas with metatases in 4 animals.

Hirsch and Russell (14) reported the case of a furniture manufacturer who died with chronic progressive induration of both lungs which had the microscopic picture of lipoid pneumonia. Extraction of the lungs with alcohol ether yielded a large amount of shellac-like material which when injected into rabbits caused necrosis and a marked exudative and fibroblastic inflammation of the lung.

The steady increase in the use of sulfa drugs and other antibodies has produced fatal lesions which have been studied by the pathologist. Black-Schaffer (15) summarized the changes found in 5 cases of fatal sulfonamide intoxications as follows: vascular lesions ranging from intramural edema to necrosis of vessel walls, and cellular exudates in skin, renal pelvis, mediastinum, gastro-intestinal tract, and other organs showing macrophages in the stage of active phagocytosis. The author believes that both types of lesions are identical with those found in experimental protein anaphylaxis.

Herbut and Scaricaciottoli (16) reported two fatal cases following sulfadiazine administration. They too emphasize the anaphylactic nature of the reaction, particularly of the diffuse hepatic necrosis.

The recent catastrophe in Boston and the use of fire as a potential weapon of war reawakened the interest in the pathology caused by excessive heat. Moritz, Henriques, and McLean (17) studied the effect of inhaled hot air on the respiratory tract. They found that the burning of the skin and mucosa of the mouth, together with fatal obstructive edema of the glottis preceded and prevented the appearance of thermal pneumonitis.

Baker (18) studied 96 cases in which cutaneous burns or complications thereof were the chief cause of death. The author emphasized the lack of specific histopathological findings and attributed most of the changes to shock, secondary infection, or in rare instances, hemoglobinemia.

III. NUTRITIONAL DISTURBANCES AND METABOLIC DISORDERS

A very interesting paper regarding the liver changes in pellagra was published by Gillman and Gillman (19). The authors performed over 600 biopsies in 120 cases of various types of nutritional deficiency. In all instances they could find evidence of liver damage ranging from minimal fatty changes to severe and progressive cirrhosis with iron pigmentation. The authors speculated upon the cause of this iron retention and came to the conclusion that it represents a sign of a disturbed mitochondrial function. They also emphasized the diagnostic importance of pigmentation with cirrhosis (pigment cirrhosis) in cases of pellagra.

The distribution of phosphatase in the liver under various metabolic conditions was studied by Wachstein (20). He found that the atrophic liver cells of starving animals and the hypertrophic liver cells of protein deficient animals showed an increase in alkaline phosphatase. Toxins disturbing the cellular metabolism, such as phosphorus and carbon tetrachloride, produced a decrease in the enzymatic activity of the injured lever cells.

Fitzgerald and Kinney (21) reported a case of rare metabolic disorder: intestinal lipodystrophy, or Whipple's disease. The case was complicated by the presence of an acute hemolytic anemia and leukocytosis. Lindsay and Knorp (22) studied a case of primary systemic amyloidosis, a condition much rarer in the United States than on the Continent.

IV. PATHOLOGY OF CIRCULATORY DISTURBANCES

The question of the importance of cholesterol in the production of arteriosclerosis was reopened by Pollak (23), who demonstrated that the lesions produced in the rabbit aorta are comparable to the lesions in the human. Ligation of both carotid arteries, both jugular veins or of one carotid artery and one jugular vein

produced lesions in the brain suggestive of hypertension. Those changes differ from the atherosclerotic lesions and can be explained by the impairment of the rate of blood flow with concomitant changes in the intravascular tension.

Interesting experiments in the field of hypertension are the successful attempts of Dick (24) to produce high blood pressure in dogs by injecting intravenous doses of live streptococci from various sources. The kidneys showed the picture of benign nephrosclerosis with scarring of the surface, fibrosis of glomeruli, and atrophy of tubules.

Flory (25) found 9 cases among 267 autopsies of persons with advanced atherosclerosis of the aorta showing evidence of embolic occlusions of smaller vessels in various visceral organs (spleen, pancreas, and kidney). He could produce the same type of lesion by injecting material scraped from atheromatous ulcerations of human aortas in the pulmonary vessels of rabbits.

Holyoke (26) studied 70 hearts with the injection technic of Schlesinger. In 12 instances occlusion of branches of the coronary vessels could be found at several points. In all hearts showing narrowing of the coronary branches interarterial anastomoses could be demonstrated. The author believes that the prompt establishment of such anatomosis could minimize greatly the danger of myocardial infarction in case of coronary occlusion. It is his opinion that other factors than simple coronary occlusion must play a part in the production of myocardial scars.

The importance of proper peripheral circulation was stressed in a study on the pathology of trench foot by Friedman (27). He concluded that all injuries resulting from exposure to low temperature followed the same train of events. A disturbance in the circulatory mechanism leads to stagnation of blood in the smaller vessels with thrombosis and gangrene, which then becomes complicated by secondary infection. Permanent changes produced in these vessels by the first exposure is the cause for the delayed sensitivity to cold temperature.

V. DISEASES OF UNKNOWN ETIOLOGY

In the field of diseases of unknown origin we may quote two studies which although they failed to prove the etiology advanced our knowledge of the diseases.

Bevans (28) studied intensively two cases of generalized scleroderma. In addition to the typical skin lesion she found myocardial fibrosis, perivascular and peribronchial fibrosis of the lung, and extensive vascular lesions in the medium sized and smaller arteries of the kidney. There were also present an atrophy of the smooth muscle of the esophagus and patchy atrophy of the smooth muscle tissue throughout the intestinal tract. The author emphasized the vascular lesions and degenerative changes of smooth muscle tissue as important factors in the pathogenesis of the disease.

Bayley, Lindberg and Baggenstoss (29) reported the first case of Loeffler's syndrome which came to autopsy. The syndrome, described in 1932, is characterized by a transitory pulmonary lesion which is usually interpreted as pneumonia, peripheral eosinophilia, and a good prognosis. A 59 year old woman complained of severe cough, restlessness and anorexia. Her blood count showed 35% eosinophils, and the x-ray picture showed dense shadows in both upper lobes. The patient improved but recurrence of her symptoms brought her back three months later. Death occurred five days after her second admission. The histological examination of the lungs showed nodular areas of fibrosis, eosinophilis, plasma cells, lymphocytes and some giant cells. Necrosis of medium sized and small arteries and veins was found with an exudate consisting largely of eosinophils and plasma cells. No evidence of a microorganism could be found bacteriologically or histologically.

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RECENT ADVANCES IN OBSTETRICS AND GYNECOLOGY

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It has been said and repeated over and over again that "there is nothing new under the sun," and so it seems to be, with what appear to be the recent discoveries and advances in this particular field. There have been some re-discoveries of old principles and re-application of these principles to modern obstetrics and gynecological surgery. There has been the application of relatively new things in the field of general medicine and surgery to this particular specialized field. There has been, too, the popularization of methods which have been preached and advanced by men of other years, yes, even of other generations, so that they are in common use today, whereas, five years ago they were considered either obsolete or the use of them, by a few scattered individuals, as the first signs of senility or psychosis. Indeed, there are not only a few if any new discoveries in this field, but in some instances a few steps "backwards" may be interpreted as a distinct advance. And I refer particularly to the discontinuance of the promiscuous use of the heterogenous gonadotropic hormone preparations clinically for their supposed beneficial effect upon the human ovary, as regards the stimulation of an abnormally functioning or a hypofunctioning ovary, as far as ovulation or the restoration of normal cyclic metabolism is concerned (1). A very few years ago these substances, particularly the equine gonadotropins and their use was reported with great enthusiasm as a distinct advance in the field of gynecological endocrinology. The use of these substances may cause far greater harm than any temporary good. They are still promoted by some commercial institutions and are still used by some inexperienced clinicians, but their large scale use has, in all medical centers, long since been dropped.

However, there has been some advance in the management of functional irregularities of uterine bleeding. It has been conclusively shown that the use of Vitamin B complex used without any specific endocrine therapy will bring about a cure in a large percentage of instances. It is interesting to note that some years ago, before the advent of specific endocrines for the management of this type of case, the treatment of the anemia, which was associated with profuse menstrual bleeding, had a beneficial effect, and this was particularly true in those cases in which the anemia was treated with crude liver extract. As the liver extract was purified more and more it was found that the beneficial effect diminished, in fact, it was almost negligible insofar as the menstrual function was concerned. It was also found that a fat soluble by-product of the purification of liver extract seemed to contain a factor which also had a beneficial effect upon menstrual dysfunction, and especially upon a profuse menstruation. It was felt that this was the substance responsible for the change brought about by the use of crude liver extract. However, it is our experience that Vitamin B complex produces much better effect than this so-called antimenorrhagic factor derived from the liver. It might then not be too far fetched to suppose that part of the beneficial effect attributed to the liver extract could have been due to an increased intake of the Vitamin B complex. Vitamin B complex in this particular aspect has been used alone or can be used only as an adjunct to the standard attack, that is the use of thyroid substance, attention to diet, exercise, and the like.

In the field of cancer control generally, and especially in the detection of early cancer in the so-called inaccessible organs and with particular reference to the educational campaign there has been a very great step forward in the early detection of cancer of the cervix. This has been championed by Dr. MacFarlane and others in Philadelphia (2) and more recently by a Chicago group (3). Their work

is worthy of report here. They undertook to determine the value of periodic pelvic examinations for the detection of cancer of the cervix in an early and curable stage and in the detection of imflammatory lesions of the cervix which may predispose to cancer. By means of appeal to patients, women's clubs, nurses' auxiliaries, social service agencies and the public at large through the press, 1,319 volunteers were found. All were presumed to be well. They volunteered to come for examination twice a year for five years as a contribution to medical science. The examination, intentionally, was kept so simple that it could be duplicated by any physician and consisted of a careful bimanual examination and a careful inspection of the cervix in a good light. Up to May 15, 1944, 9,111 pelvic examinations had been made. In the first examination of these volunteers, early cancer of the cervix was discovered three times. The fact that these three cancers of the cervix were discovered in areas of papillary erosion and not in healthy non-inflammatory cervices was significant and lends great support to the theory that cancer can develop in these so-called areas of epithelial unrest. At the Chicago Clinic, of the first 600 patients examined, ten were found to have cancer of the cervix. Erosions of the cervix were found in 75 cases, with treatment advised, and two cancers were found elsewhere in the female generative tract. The calling attention of these facts to the medical profession and to the public at large may result in the distinct advance of cancer control in regard to the female genitalia, but the real advance will only be made when the laity and the profession are taught that early uterine cancer is cureable; that time is important; that hormones do not cure all gynecological disorders; that menstrual irregularities during the menopause are not normal; that irregular vaginal bleeding at any age may indicate early carcinomatous changes, or that unexplained vaginal bleeding, especially post-menstrual bleeding, can be caused by cancer and does not always result from endocrine deficiency, fibroids and the like, although they may be associated with them, and that vaginal discharge in adults may be an early sign of a malignant condition. In regard to the treatment of cancer of the cervix, it is a well known fact that it has always been generally unsatisfactory, even in early tumors. The original Wertheim operation for carcinoma of the cervix as practiced, perhaps before the advent of what we may consider now newer surgical technique and post-operative care, carried with it too high a mortality rate. Its favor gave way to radiation therapy entirely in many clinics and in fact the surgical treatment of cancer of the cervix has been until recently frowned upon by many. As the actual matter of fact, the result of the radiation treatment of cancer of the cervix has actually been no more satisfactory, except that the initial operative mortality was extremely low, but in those individuals who are not cured, the mortality rate from the cancer was still 100 per cent. There has been a constant search, of course, for the ideal method of treatment. Taussig brought forward, several years ago, the combination of irradiation with radical dissection of the lymphatics draining the cervix. By this combination therapy, he felt that his results were better. More recently there has been restated the argument for surgical treatment of cancer of the cervix, especially by Dr. Meigs of Boston (4). He has combined the original Wertheim radical excision of the internal female genital organs with the pelvic operation for excision of the lymphatics. Meigs has reported an astounding survival rate of 96.3 per cent in cases in which there was no lymph node involvement by this operation and a corrected survival rate of 87.7 per cent of all cases. These are undoubtedly by far the best results obtained by radical operation for cancer of the cervix.

Recently reported (5) has been the extremely high incident of all types of congenital anomalies, probably most frequently occular and cardiac defects in babies born of mothers who has contracted rubella or German measles during the early months of their pregnancy. It is generally conceded that 100 per cent of mothers who contracted rubella the first two months of pregnancy will give

birth to infants with some form of congenital anomoly, and about 50 per cent of mothers who contract rubella in the third month have abnormal babies. It is considered by some a very definite indication of therapeutic abortion if the mother has contracted rubella during the first two months of pregnancy. Also very definitely indicated, is the avoidance of contact of women in early pregnancy with known cases of German measles. The use of immune globulin for the protection of women in early pregnancy, who have been exposed to rubella, has been advocated.

Early postoperative ambulation, as we use it today and as it is being practiced more and more, is most certainly a distinct advance in the care of surgical patients and especially in respect to abdominal surgery. The reduction of postoperative complications and a much earlier feeling of well-being by the patient are distinct advantages. The incidence of postoperative thrombophlebitis, which is especially prone to follow all types of pelvic surgery, and the incidence of pulmonary embolus, has been greatly reduced by ambulation. Abdominal distention, ileus and troublesome gas pains are also greatly reduced by early ambulation. Pulmonary complications, such as atelectasis, pneumonia, etc., are rarely seen where early ambulation is practiced. Not too long ago patients were kept in bed as long as twenty-one days following a hysterectomy. It is now practiced here and in many clinics to get the patient out of bed, or at least up on the edge of the bed, on the day of operation and to gradually increase their time up daily thereafter so that most of these individuals are ready to leave the hospital within seven to ten days.

The newer forms of chemotherapy, sulfonamides and penicillin and its related compounds have reduced the mortality rate and the long time morbidity rate of the one time dreaded child-bed fever to almost nothing. The same may be said in regards to the reduction of the incidence of breast abscess in the puerperium. In addition to this, treatment of the acute pelvic inflammatory disease in the post-abortion state and that which is primarily due to gonorrhea, with these drugs, has reduced remarkably the number of patients coming to surgery because of the sequalae of these infections. The resolution which is seen in some of these individuals with acute inflammatory disease of the pelvis is almost unbelievable, when they have been treated with these drugs, and especially the combination of the sulfonamides and penicillin.

Continuous caudal anesthesia has become quite popular in many clinics in the past five years and has been rather widely used. This is shown by the fact that over 100,000 deliveries with this method have already been recorded in the literature (6). This method is not, however, without danger and disadvantage. It is a highly specialized form of anesthesia and entails among its dangers, death. Briefly, it is a method devised to maintain continuously access to the caudal canal through which an anesthetic agent can be administered intermittently during labor and over a relatively long period of time. The chief advantage of continuous caudal anesthesia are the absence of depression in the baby, low toxicity to the mother and the complete absence of pain during the uterine contractions and delivery.

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RECENT ADVANCES IN CARDIOVASCULAR DISEASES

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In the field of congenital heart malformations, several recent advances in treatment have altered our approach to what was once considered a hopeless problem. Some years ago Gross first introduced surgical intervention in the treatment of a patent ductus arteriosus. This communication between the aorta and pulmonary arteries normally closes shortly after birth. The persistence of a patent duct seriously alters normal adult cardiovascular dynamics. Although some patients live a comfortable life, most of them develop subacute bacterial endocarditis or progressive congestive heart failure. Gross (1) conceived and perfected the surgical technique of ligating the patent ductus with a minimum of operative risk. Although the procedure is not always technically possible, the results in a great majority of patients are highly gratifying. The indications for surgery are subacute bacterial endocarditis or beginning cardiac embarrassment.

Within the past two years Blalock and Taussig (2) conceived the idea that perhaps an arterial shunt could be created to circumvent a congenital stenosis of the pulmonary artery or valve. The children suffering from this lesion are pitiable creatures, with their intense cyanosis, severe dyspnea and clubbed fingers. The technique, after careful experimental studies, was finally carried out in children with an otherwise hopeless prognosis. It consisted of anastomosis of a large arterial branch of the aorta to the pulmonary artery or one of its main branches beyond the point of stenosis. Preliminary reports are very encouraging.

Gross and Hufnegel (3) have reported resection of the area of atresia for correction of coarctation of the aorta. This procedure involves much more difficult surgery and there is no series of cases to present as a basis for discussion. But the ice has definitely been broken and much more accurate differential diagnosis of congenital heart lesions is desirable in order to uncover those that might now or in the future be amenable to surgery.

There have been several recent advances in the field of acute rheumatic fever and rheumatic heart disease. Most reports indicate a favorable response in the prevention of acute rheumatic fever by small daily doses of Sulfadiazine. An average of 0.5 to 1.0 grams daily is considered as adequate dose. Toxic reactions are few but the blood count should be followed at frequent intervals. There is some question concerning the development of sulfa-resistant strains of streptococci; this problem has not been settled. However, we do know that sulfa drugs are contraindicated during or within three months after an attack of acute rheumatic fever. The possibility of applying the same principle to the use of oral penicillin offers hope in the future of perhaps several agents to reduce the acute recurrence of this disease.

Coburn (4) has re-opened the question of the therapeutic value of salicylates in the treatment of the acute stage of rheumatic fever. He has recently treated a series of cases with massive doses of salicylates and is convinced that cardiac involvement is lessened and the duration of the acute stage shortened. This also re-opens the question of the fundamental effect of salicylates on antigen-antibody reactions in the body and, hence, on the prophylactic as well as therapeutic effect of salicylates on the hypersensitive rheumatic fever patient. There is not general agreement on this subject but the prospect of a more favorable course of the acute disease appears to be worthy of close scrutiny.

The past two years have seen the only real advance in the treatment of subacute bacterial endocarditis. Before the use of penicillin, I had never seen even one patient recover from this disease but in the past two years have indicated

recovery in 25 to 75 per cent (5). The dosage of penicillin necessary, the methods of administration and the length of treatment have been pretty well worked out. Three hundred thousand to one million units daily by continuous intravenous or intrasternal route for a period of six weeks seems at this time to be the most satisfactory regimen. The most important points to be remembered are: 1, the earlier the diagnosis is made the better the prognosis; 2, the daily dose should be optimum rather than minimum; 3, treatment should be continued for several weeks after negative blood cultures have been obtained, and 4, anticoagulants are of no value in the therapy and are in fact definitely contraindicated.

The prevention of subacute bacterial endocarditis following nasal and oral surgery and extraction of teeth in known rheumatics is an equally great stride in therapeutics. Perhaps it would be proper to say that it is more important than treatment of the disease. Sulfadiazine 1 gm. every four hours for twenty-four hours before and forty-eight hours after such procedures is the present method of choice. It should be routine practice to stress to all our known rheumatics the dangers involved and the importance of proper prophylaxis even though the extraction of a tooth may seem a trivial procedure. Perhaps in the future oral penicillin will supplant sulfa drugs.

In spite of intense study of the causes and treatment of hypertension by many investigators, there is little for me to report. The status of medical treatment has changed but little. Surgical treatment by sympathectomy has been the subject of much controversy; some patients so operated have seemed to respond nicely whereas others presenting a nearly similar clinical picture have not. In the past the cold pressor test, the pentothal anaesthesia test and spinal anaesthesia test have been used singly or in combination in an attempt to select for surgery those cases which might, on the basis of the results of the tests, be expected to show optimum improvement. Postoperative results have not been uniform. Russek, Southworth and Zohman (6) recently reported a new procedure for the prediction of a favorable or unfavorable response to sympathectomy. Their method employs the use of continuous caudal anaesthesia which may be maintained at any segmented level. The results of blood pressure determinations during anaesthesia are reported as a reliable index of the response to surgery in approximately 90 per cent of cases.

Wright (7) reported recently of a neurovascular syndrome due to hyperabduction of the upper extremity. He found changes in the pulse in approximately 84 per cent of normal young males when the upper extremity was placed in this position. Some of these complained of numbness, tingling and pain when the arm was maintained in this position for even short periods of time. Wright felt that most persons would return the arms to normal position even during sleep but he reported several cases which had severe day-long disability due to continued maintenance of hyperabduction during sleep. One of his cases had tropic changes in the finger tipe because of prolonged interference with circulation. The etiology is distinct from the scalenus anticus syndrome and results from the pinching of the subclavian artery and brachial plexus between the first rib, pectoralis muscle and clavicle when the upper arm is hyperabducted.

In the treatment of congestive heart failure, I feel there has been a recent very outstanding advance, one which will help to clear up some of the confusion about variation of potency of various digitalis preparations. Crystalline Digitoxin is available in tablet and ampule form under various trade names. In contrast to oral digitalis leaf this preparation is completely absorbed in the G-I tract and 100 per cent of the drug administered is utilized; it causes very few undesirable symptoms such as malaise, anorexia, nausea and vomiting. Massive single-dose oral or intravenous digitalization can be easily accomplished as a routine measure with great safety. The dose is 1.2 mgm. to 1.6 mgm. or six to eight tablets; maintenance dose is 0.1 mgm. or 0.2 mgm. or one-half to one tablet. In my experience it is tolerated by elderly patients much better than digitalis leaf.

It is probably the best product for routine use because of ease of dose calculation, ease of administration and better tolerance.

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PHYSIOLOGY

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In this paper an attempt will be made to describe some of the recent advances in the physiology of both the nervous system and the endocrine glands. While the peculiar interests of the author dictated the selection of material, it is hoped the subjects chosen are of general interest.

The pituitary-adrenal control of the release of antibodies from lymphoid tissue.

One of the more interesting recent contributions to physiology has been the demonstration of a functional relationship between two of the endocrines and the activity of lymphoid tissue. Since the present concepts are based on seemingly unrelated investigations in fields far-removed from each other, it is considered desirable to briefly review the more important points upon which these ideas are based.

As a result of careful correlation of the isolated data of previous workers and crucial experiments of his own, Selye, 1936, introduced the concept of an "alarm reaction," a typical series of events taking place whenever the organism is subjected to severe stresses or damaging agents. (1) As a part of this reaction the lymphoid tissues, lymph nodes, thymus and spleen undergo involution, while the adrenal cortex hypertrophies. It was also established by Selye (2) that the lymphoid tissue changes in the alarm reaction do not take place if either the pituitary or adrenals are absent. The nature of this dependence of the lymphoid tissue on the adrenal and pituitary was shown by Dougherty and White (3) who found that anterior pituitary corticotrophic factor caused atrophy of the lymphoid tissues when injected into intact animals, but not when administered to adrenalectomized animals. They further found that administration of adrenal cortical extract or corticosterone causes involution of lymphoid tissue. These facts taken together with the histochemical finding of a greater secretory activity of the adrenal (3, 6) during the alarm reaction, show that the lymphoid tissue involution comes about because of an increased output of adrenal hormone, the release of which is under the control of the pituitary.

The story does not end at this point, for it has also been observed that a lymphopenia accompanied by an increase in the concentration of the plasma proteins occurs during the alarm reaction (3, 4, 5). The lymphopenia is accounted for by the failure of the involuting lymphoid tissue to deliver ample lymphocytes to the blood stream because of liquefaction and dissolution of stored lymphocytes, while the increased plasma protein is considered to come from the destroyed lymphocytes. Electrophoretic studies have shown that this extra plasma protein consists largely of anti-body containing gamma globulin (6). Confirmation of the importance of the lymphocytes as producers of antibodies has come from the work of Harris et al. (7) and Rich, Lewis and Wintrobe (8) who employed immunological techniques. When these latter findings are taken into account it may be finally said that the pituitary acting through its influence on the adrenal controls the release of antibody globulin from the lymphoid tissues.

Relationships between hormones and enzymes.

An approach to the problem of the mechanisms by which hormones really exert their effects has been made through the study of hormone-enzyme relationships. The logic for undertaking such studies is clear when one considers the fact that hormones alter the metabolism of tissues and that enzymes are ultimately responsible for the energy transfers involved. Since changes in the concentrations of enzymes might well account for the changes in metabolism, the concentrations of various enzymes have been studied in different endocrine states. A number of such relationships have already been demonstrated, e.g., the concentration of cytochrome-c decreases after adrenalectomy and can be restored by the administration of adrenal cortical extract (9), liver alkaline phosphatase concentration is increased in dogs with alloxan diabetes (10) and estrogen injections lower the serum acid phosphates in intact animals (11). Since only a few enzymes in but a small number of endocrine states have been investigated, one expects to see much activity in this field in the future.

One should not leave a consideration of the hormone-enzyme relationships without mentioning the vitamins, several of which (nicotinic acid, thiamine, riboflavin and possibly ascorbic acid) go into the make-up of enzymes and co-enzymes (12, 13, 14). Furthermore, it is known that deficiencies in these vitamins result in lowered concentrations of certain enzymes and co-enzymes and thus decreases in the metabolic activities dependent upon them (12, 13, 14). In view of the fact that the levels of both hormone and vitamin exert an influence on the concentration of enzymes, it is apparent that much future investigation should be carried out to determine the details of the relationships between these three substances.

Adrenal ischemia and hypertension.

It has recently been found that unilateral subtotal ligation of periadrenal blood vessels and tissues results in the development of an hypertension, which is apparent after one to three days and which lasts for months (15). In view of the important facts emerging from the study of the ischemic kidney, one expects thorough exploitation of this ischemic adrenal preparation.

Acetylcholine and conduction of the nerve impulse.

During the past few years a theory relating acetylcholine to the conduction of impulses along nerve fibers has arisen. The facts upon which the theory is based are: (a) Nerve fibers contain and can synthesize acetylcholine (16), (b) nerve fibers contain cholinesterase (17), (c) acetylcholine possesses the ability to depolarize membranes (18, 19, 20). The theory states that the stimulus to the nerve fiber results in the release of acetylcholine which depolarizes the neural membrane rendering it permeable to all ions; this results in the generation of an

action potential which stimulates the adjacent region of the neuron and brings about the release of acetylcholine there, thus repeating the whole process. The cholinesterase present destroys the acetylcholine allowing the membrane to recover its polarization.

The authors of recent experiments (21, 22) suggest a drastic modification of this theory. They state that the action potential is due solely to acetylcholine and that the old Bernstein theory of the polarization of the neural membrane by inorganic ions is untenable.

Synthesis of acetylcholine.

Much recent work has been done to show that the synthesis of acetylcholine by brain and nerve depends upon the presence of both adenosinetriphosphate and an enzyme, cholineacetylase (23).

The autonomic nervous system.

Brief mention should be made of a new concept of the functions of the sympathetic and parasympathetic systems in dually innervated organs. The old ideas of the dual innervation by the sympathetic and parasympathetic systems and the functional antagonisms of these two systems appear to be false. In dually innervated structures such as the iris, the gastro-intestinal tract and the urinary bladder, it has been shown that the sympathetic system exerts its influence solely on the blood vessels and the parasympathetic through actual innervation of the smooth muscle of the organs (24, 25, 26).

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RECENT ADVANCES IN OTO-LARYNGOLOGY

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The most striking advances in Oto-Laryngology in the past year have been in the use and administration of Penicillin and the application of radium to the naso-pharynx.

Aerotitis is due to the inability to ventilate the middle ear. Otalgia is the first symptom, and may be so severe as to cause unconsciousness, shock, nausea, vomiting and vertigo. Labyrinthrine damage seems inevitable with such a violent accident. After pain subsides, there remains a loss of hearing with stuffiness or pressure deep in the canal (1).

Appearance of the drum parallels the symptoms. The membrane tympani is usually hemorrhagic and retracted. Hemorrhage may be in the drum or in the middle ear. The hemorrhage changes color with time, becoming a deep red and later a dark blue, while the ossicles stand out white against this background. It takes about three weeks to recover.

Hearing loss is a prominent symptom. There is no characteristic curve but the type of deafness is conductive with a negative Rinnee and Weber is lateralized to the involved ear.

Serous otitis may follow, fluid accumulates under negative pressure and it may shift with the change of position of the head. This changes the hearing as it leaves the vital structures.

The hyperplastic lymphoid tissue in the naso-pharynx is the most common cause of eustachian tube malfunction. Lymphoid tissue regresses after radium therapy about the eustachian tube. It removes not only the mechanical factor which predisposes to aerotitis, but also tissue that harbors pathogenic organisms that precipitate attacks of naso-pharyngitis. This lymphoid tissue about the eustachian tube is the most common cause of conductive deafness in children and predisposes to repeated attacks of otitis media. Of 6,881 (2) men, 74% were benefited and 89% showed a marked decrease in adnoid tissue, definite improvement in hearing, and in the ability to ventilate the middle ear.

Dr. Lempert (3) offers a new theory and suggests that tinnitus aurium in many cases and under certain conditions may be due to a tonus impulse transmitted to the inner ear by disease of the sympathetic ganglion cells of the tympanic plexus. Based on this new theory, Tympano-Sympathectomy is recommended for the relief of tinnitus aurium.

A surgical technic by which Tympano-Sympathectomy may be performed without disturbing the hearing has been successfully employed.

Not all cases of tinnitus are embraced by this theory, and there is no definite way as yet to select the cases which apply. Nevertheless, of fifteen patients on which Tympany-Sympathectomy was performed, ten are now completely free from tinnitus. Patients selected had severe, persistent tinnitus for one year duration or more, and were unable to concentrate because of its intensity.

Dr. Lempert (4) reports over 1,000 patients with clinical otosclerosis that have been treated by fenestration of the labyrinth in the last seven years. In the last 700, the fenestra nov-ovalis was created in the surgical dome of the vestibule. Practical, serviceable hearing for all social and economical purposes was restored and continuously maintained in about 50% of the cases.

Closure of the newly created fenestra by new bone formation, and damage to the organ of Corti as a result of serous labyrinthitis, were found to be the two major obstacles. Bone formation may be stopped by cartilage stopple.

Day (5) reports approximately 80% of patients get serviceable hearing if one selects patients under forty-five years of age and with bone conduction of not less than 15 decibels in speech range. He does not use cartilage stopple.

Shambaugh (6) has an average of 25.7 decibels improvement in 321 cases operated, using the nov-ovalis technic of Lempert modified by constant irrigation of the field and the use of the binocular dissecting microscope while the fenestra is being made.

If a mastoid is operated, closed and a ureteral catheter placed in the mastoid, then irrigated with 10,000 units of Penicillin of 2 c.c. volume every eight hours for four days, it will be completely cured as reported in eighteen of the twenty-three patients tried (7).

External otitis is often a difficult disease to treat. This is due to fungus infection, humidity, temperature and secondary infection by different organisms. Thymol 1% in Cresatin will control 80% of the fungus cases, and the cellulitis of the canal will respond to Chemotherapy if gram positive organisms are present. Some of the foulest ears are sulfa resistant and are infected with *B. pyocyaneus*, which will respond in 48 hours upon packing with 5% Sodium Thiosulfate (8), followed by a 2% Acetic Acid pack for five minutes. This must be continued for several days to prevent recurrence even though the canal looks normal.

Penicillin solution of 250 units per c.c. has no effect on the ciliary beat, which normally lasts from 25–28 hours. Using 500 units per c.c., the ciliary beat was reduced to 15–19 hours; 5,000 units per c.c., the beat was reduced to 3–6 hours. Therefore, a weak solution of Penicillin has no damaging effect on the cilia or epithelium of respiratory mucosa (9).

Two c.c. of Penicillin (10–20,000 units) with 1 c.c. of 1% Novacaine injected (10) into an early peri-tonsillar swelling will give marked relief from pain in 2–3 minutes and the patient can swallow without discomfort.

Penicillin 1–300,000 units, single dose per day, in peanut oil and .02 gm. Novacaine has proven very satisfactory as an office procedure to combat infections caused by Penicillin sensitive organisms. This leaves the patient ambulatory, quick recovery and no side reactions except delayed sore arm in some patients. Otitis media, serous otitis, acute sinusitis, septic throat and vincents, all respond faster than those cases in which sulfa was used.

J. R. Richman (11) reported a new treatment for esophageal obstruction due to meat impaction. There were 17 cases treated by oral ingestion of a proteolytic enzyme, papain powder. Twelve were relieved in an hour and a half, some of these within thirty minutes. The papain digests thirty-five times its weight of meat. I have used this four times in the last three months in patients who were very poor risks for esophagoscopy, and all were completely relieved of the obstruction within half an hour.

In bilateral adductor paralysis following injury to both recurrent nerves, the King or Kelly operations to abduct the cords have been indicated. Murtagh (12) shows us that by cutting the external branch of the superior laryngeal nerve, which supplies the crico-thyroid muscle, the cords shift permanently to a position of abduction.

Inoperable carcinoma of the larynx may respond to X-ray therapy by Coutard method, using 4–6000 Units, after complete removal of the thyroid cartilages. Arbuckle reported 18 cases recently. I have 2 cases with complete regression of the neoplastic tissue, but only two years after treatment. This offers new hope for the advanced cases of carcinoma of the larynx.

A large proportion of patients seen in the office practice of otolaryngology suffer from chronic nasal allergy, frequently complicated by a superimposed infection. The best therapeutic results can be obtained when treated simultaneously. History, stained nasal smears, skin tests, elimination diets, and therapeutic tests,

aid in the diagnosis of nasal allergy. Sensitivity to house dust is more frequently encountered than generally recognized and the therapeutic response to it, is very satisfactory in a great majority of cases.

Aerosinusitis is an acute or chronic inflammation of one or more nasal accessory sinuses, produced by barometric pressure difference between air inside the sinus and that of the surrounding atmosphere, and it must be differentiated from purulent and catarrhal sinusitis. History of a recent flight is often a deciding factor but X-ray, disclosing opacity or thickened membrane in absence of previous sinusitis, sudden pain over the sinus, epistaxis, during or after exposure to baratrauma, and no previous rhinitis, is extremely suggestive. Aerosinusitis usually responds to vaso-constriction, but polyps or other obstruction must be eliminated, and at times Caldwell-Luc is necessary.

In the management of chronic sinus diseases, simple measures, if properly applied, suffice in 97% of the cases. Attention is concentrated on the drainage area of involved sinuses and all efforts are directed toward restoration of function of the ostca. In most cases of few months duration, the opening itself is not at fault, but rather, the trouble lies in relation of adjacent tissue to the opening. The defects may be anatomic or pathologic. Most common is a blocked middle meatus by an impinging middle turbinate wedged against the lateral wall, septal deviation, spurs, cellular turbinate, etc. In pathological groups, edema from allergy is most prominent in which case the mucus membrane may swell 50 times its normal thickness in a few hours and easily block the ostium. Swelling may be a Vasomotor reaction to an endocrine imbalance, G.I. disturbance, or some other systemic condition.

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BOOK NOTICES

A New Text Book of Genetics

There is a very complete presentation of modern genetics, written by one who had the good fortune to be a member of the Drosophila group at Columbia University during the formative years of the science. Although Drosophila is used to a large extent throughout the book, many examples from human inheritance are interspersed, as well as instances from domestic and laboratory animals, and plants. The style is clear and simple, and the book is written with the viewpoint of the student continually in mind. Excellent drawings and diagrams clarify all difficult points.

The Drosophila system of gene nomenclature is used, a fact which in the opinion of this reviewer offers the greatest drawback to the usefulness of the text. Fortunately all geneticists do not share this writer's aversion to the + as a gene symbol. Excellent summaries follow the texts of the chapters, and well thought out problems are appended to each chapter. No references are given. A few typographical errors appear, but the book is remarkably free from them. Particularly good discussions are presented of chromosomal aberrations, mutations, and the bearing of genetics on development and evolution. The book is as complete and modern as a text could well be.—*L. H. Snyder.*

Genetics, by Edgar Altenburg. xii+452 pp. New York, Henry Holt and Co., 1945.

Check List of Cicadellidae

The first attempt at bringing together the species of the family Cicadellidae since the publication of the catalogue by Van Duzee in 1917 appeared in mimeograph form in 1937 under the authorship of DeLong and Caldwell. Since then generic revisions based on structural characters have resulted in many new species and some new synonomy. All these changes and additions have been incorporated into this new recently published Check List.

It lists 175 genera and 2276 species, varieties, and subspecies occurring north of Mexico. Synonomy as given in the Van Duzee catalogue is not repeated. Original literature on each species is cited by number from a list near the end of the paper which saves repetition of wording names of journals or other places of publication. The specific names under each genus are alphabetized which simplifies the locating of a particular species.

A suggested list of generic papers on the family and an index to genera completes the publication.

This is an invaluable tool for those interested in classification of insects and especially those who are actively engaged in studies on the taxonomy of leafhoppers.—*Ralph H. Davidson.*

Check List of the Cicadellidae (Homoptera) of America, North of Mexico, by Dwight M. DeLong and Dorothy J. Knull. 102 pages. 1945. Ohio State University Graduate School Studies. Biological Science Series No. 1. Paper bound. $1.50.